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Review

Pharmacology of *Schisandra chinensis* Bail.: An overview of Russian research and uses in medicine

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ABSTRACT

Schisandra chinensis (Turcz.) Bail. is often referred to as an example of a medicinal plant with use in modern Chinese medicine. However, *Schisandra chinensis* first gained recognition as an adaptogen in the official medicine of the USSR in the early 1960s, principally as a result of the large number of pharmacological and clinical studies carried out by Russian scientists in the preceding two decades. Schizandra has now secured an established position within the medicine of Russia/USSR as evidenced by the inclusion of the drug in recent editions of the National Pharmacopoeia of the USSR and in the State Register of Drugs. Pharmacological studies on animals have shown that Schizandra increases physical working capacity and affords a stress-protective effect against a broad spectrum of harmful factors including heat shock, skin burn, cooling, frostbite, immobilisation, swimming under load in an atmosphere with decreased air pressure, aseptic inflammation, irradiation, and heavy metal intoxication. The phytoadaptogen exerts an effect on the central nervous, sympathetic, endocrine, immune, respiratory, cardiovascular, gastrointestinal systems, on the development of experimental atherosclerosis, on blood sugar and acid–base balance, and on uterus myotonic activity. Studies on isolated organs, tissues, cells and enzymes have revealed that Schizandra preparations exhibit strong antioxidant activities and affect smooth muscles, arachidonic acid release, biosynthesis of leukotriene B_4 in leukocytes, platelet activating factor activity, carbohydrate–phosphorus metabolism, the formation of heat shock protein and polyamines, tissue respiration and oxygen consumption, and the tolerance of an organism to oxygen intoxication. In healthy subjects, Schizandra increases endurance and accuracy of movement, mental performance and working capacity, and generates alterations in the basal levels of nitric oxide and cortisol in blood and saliva with subsequent effects on the blood cells, vessels and CNS. Numerous clinical trials have demonstrated the efficiency of Schizandra in asthenia, neuralgic and psychiatric (neurosis, psychogenic depression, astheno-depressive states, schizophrenia and alcoholism) disorders, in impaired visual function, hypotension and cardiotonic disorders, in epidemic waves of influenza, in chronic sinusitis, otitis, neuritis and otosclerosis, in pneumonia, radioprotection of the fetoplacental system of pregnant women, allergic dermatitis, acute gastrointestinal diseases, gastric hyper- and hypo-secretion, chronic gastritis, stomach and duodenal ulcers, wound healing and trophic ulcers. This review describes the considerable diversity of pharmacological effects of *Schisandra chinensis* reported in numerous studies carried out in the former USSR and which have been confirmed over more than 40 years of use of the plant as an official medicinal remedy. Such knowledge can be applied in the expansion of the use of Schizandra in the pharmacotherapy of European and other countries as well as for the further discovery of new drugs based on the lignans that constitute the main secondary metabolites of this plant.

Abbreviations: ACTH, adrenocorticotrophic hormone; ADS, astheno-depressive syndrome; ARD, acute respiratory disease; CFLF, critical frequency of light flashes; CNS, central nervous system; CYP3A4, cytochrome P450 3A4; ECG, electrocardiogram; ED, effective dose; FPS, fetoplacental system; HETE, hydroxy-eicosatetraenoic; HPA, hypothalamus–pituitary–adrenal; HPLC, high pressure liquid chromatography; IC, inhibitory concentration; IL-2, interleukin-2; i.p., intraperitoneal; LTB4, leukotriene B_4; NO, nitric oxide; PAF, 1-*O*-Alkyl-2-acetyl-*sn*-glycerol 3-phosphocholine; p.o., per-oral; pSAPK/p-JNK, phosphorylated stress-activated protein kinase; PWC, physical working capacity; SSE, Schizandra seed extract; SSP, Schizandra seed powder; ST, Schizandra tincture; TLC, thin layer chromatography; USSR, Union of Soviet Socialist Republics; UV, ultraviolet.

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Contents

1. Introduction

Schisandra chinensis (Turcz.) Bail. is often considered to be an example of a medicinal plant with a use in modern Chinese medicine. However, the contemporary applications of Schizandra result primarily from a large number of pharmacological and clinical investigations carried out in the former USSR during the period 1940–1960. Studies of *Schisandra chinensis* were initiated in Russia during the Second World War by command of the People's Commissar Council with the stated objective being "to study the Chinese herb Limonnik with the purpose of determining its possible use as a raw material for obtaining organic acids, ether oils and tonic substances" (order 4654-p dated 4.3.1943) (Lebedev, 1967). Extensive research revealed, however, that extracts of Schizandra possessed important stimulatory effects, and on this basis *Schisandra chinensis* achieved recognition in the official medicine of Russia in the early 1960s. In order to emphasise the significance of this event it should be noted that, up until 1978, less than 60 plant-based preparations had been officially accepted into Russian medicine despite the existence in the USSR of large numbers of plants with ethnobotanical applications (Mashkovskij, 1978, 2000). Thus, whilst the health services in the USSR and Europe were similar in all essential respects at this time, a far larger number of plant-based medications were recognised in the official medicines of Germany and France than in Russia.

Since 1960, Schizandra preparations have secured an established position within Russian medicine, and specific monographs for fruits and seeds of *Schisandra chinensis* have appeared in various editions of the National Pharmacopoeia of the USSR (1968a,b, 1990). Recent State lists and registers of medicines and drugs (The Ministry of Health and Medical Industry of Russian Federation, 1997, 2000) include a number of medicines based on *Schisandra chinensis* that are currently produced in Russia, namely, Tinctura Schizandrae, Fructus Schisandrae, Tinctura Fructum Schizandrae, Semen Schizandrae and Schizandra tablets.

In consideration of the above, it is perhaps not surprising that much of the literature relating to a broad range of studies on Schizandra has appeared in Russian journals (Fig. 1). Thus, 470 of the 552 references included in the bibliographic sections of a series of three articles on *Schisandra chinensis,* published in *Aptechnoye Delo* by Senov between 1927 and 1959 (Senov, 1952, 1953, 1959), are in Russian. Somewhat limited accounts of the specific properties of Schizandra are available in English in various reviews of plant adaptogens (Brekhman and Dardymov, 1969; Wagner et al., 1994, 1996; Panossian et al., 1997, 1999a,b), but an enormous amount of detailed information contained in a number of key articles in Russian (Brekhman, 1951; Sorokhtin, 1955; Sorokhtin and Minut-Sorokhtina, 1958; Lebedev, 1971a; Lapajev, 1978; Lupandin and Lapajev, 1981; Lupandin, 1989a,b, 1991) remains relatively inaccessible to Western scientists. The aim of the present review is to fill this gap by summarising the extensive literature concerning *Schisandra chinensis* in a structured, if rather parsimonious, manner (Table 1). This review describes the considerable diversity of pharmacological effects of *Schisandra chinensis* reported in numerous studies carried out in the former USSR and which have been confirmed over more than 40 years of use of the plant as an official medicinal remedy. Such knowledge can be applied in the expansion of the use of Schizandra in the pharmacotherapy of European and other countries as well as for the further discovery of new drugs based on the lignans that constitute the main secondary metabolites of this plant.

Fig. 1. Number of publications concerning *Schisandra chinensis* published in Russian and those cited in PubMed between 1940 and October 2007. [a]References listed in this review.

2. General information

The genus *Schisandra* (family Magnoliaceae) consists of 25 species, two of which, namely *Schisandra chinensis* and *Schisandra repanda*, have a history of medicinal use (Gutnikova, 1951). *Schisandra chinensis* (synonyms, *Schisandra spenatera* Rehd. et Wils., *Kansura chinensis, Sphaerostemma japonica, Sphaerostemma japonicum, Maximoviczia chinensis* and *Maximoviczia amurensis*) is endemic to the northwest of China (Heilongjiang/Mandzuria), Korea, and the far east of Russia (the Primorsky, Amursky and Khabarovsky regions, the Kuril Islands of Schikitan, Kunashir and Iturup, and the Sachalin islands) (Fig. 2). A detailed map of the distribution of the species on the Sachalin and Kuril Islands is available (Fig. 3; Gutnikova, 1951; Agejenko and Komissarenko, 1960). The medicinal plant is variously known as Maximowich's red grape or Limonnik (since the leaves, bark and stem all exude an odour reminiscent of lemon) in Russian, as kocyalta in Nanai (Goldish), as gagabanku in Udeheyish, as wu-wei-zi (five taste fruit), ji-chu, or hoy tsi in Chinese, as omiza in Korean, and as gomishi in Japanese (Gutnikova, 1951).

2.1. Traditional uses in China

In traditional Chinese medicine, the curative properties of Schizandra were associated with the five tastes, i.e. sweet, sour, bitter, astringent and salty, associated with different parts of the berries. Thus, the sour and salty principles were believed to exert their effects on the liver and testicles, the bitter and stringent constituents on the heart and lungs, and the sweet components on the stomach (Fil'kin, 1952). In Chinese folklore the plant was used as a stimulant in sexual weakness and impotence, and to treat pollution, spermatorrhoea, nocturnal emission, gonorrhoea, enuresis, frequent urination, protracted diarrhoea, dysentery, impairment of body fluids, spontaneous sweating, night sweating, cough, asthma, phlegm, wheezing, jaundice, thirst, shortness of breath, feeble pulse, urinary tract disorders, body weakness, exhaustion, diabetes

Table 1
Main historical dates in the development of *Schisandra chinensis* research in USSR/Russia

Milestone	Year	Reference
First ethnobotanical, botanical and phytochemical studies	1927–1952	Fil'kin (1952)
Bibliographical study of 452 references		Senov (1953)
First chemical studies	1940	Balandin (1940)
First pharmacological study on animals	1942	Drake (1942)
People's Commissar Council issues Official Order Nr 4654 dated 4.3.1943 "to study the Chinese herb Limonnik with the purpose of determining its possible use as a raw material for obtaining organic acids, ether oils and tonic substances"	1943	Lebedev (1967)
Validation of the traditional use of Schisandra fruit by Nanai hunters: stimulating effect on physical working capacity in humans	1943–1945	Astanin et al. (1943); Karo (1945); Yefimov and Vlasova (1945); Murtazin (1946); Lazarev (1946)
Validation of traditional use of Schisandra fruit by Nanai hunters	1948	Galochkina (1948)
Improvement of visual function of aye and night vision in humans	1953	Trusov (1953)
First clinical trials of Schizandra in depression	1946	Staritsina (1946)
Introduction of State Standards on Quality of Schizandra fruit and seeds	1947, 1950	Zemlinskij (1958)
Estimation of natural recourses in the Far East and start of cultivation	1951	Gutnikova (1951)
Isolation of the active principle schizandrin	1951	Balandin (1951)
Stimulating effect of schizandrin in humans and animals	1951	Lebedev (1951a,b)
Elucidation of the chemical structures of schizandrin, gamma-schizandrin, and deoxyschizandrin	1962	Kochetkov et al. (1962a,b)
Total chemical synthesis of deoxyschizandrin	1962	Kochetkov et al. (1962c)
Introduction of adaptogen concept in Schizandra research	1962	Brekhman and Dardymov (1969)
First Pharmacopoeia article on Fructus Schizandrae included in the USSR National Pharmacopoeia	1968	
Industrial production of Schizandra preparations from fruit and seed in Khabarovsk and St-Petersburg Pharmaceutical factories on a scale of more than 9 tonnes per year	1968	Kolkhir (2004)
Use of Schizandra in the official medicine of USSR	1968	Turova (1974); Mashkovskij (1978)

caused by internal heat, palpitation and insomnia (Fil'kin, 1952; Kimura et al., 1996; World Health Organisation, 2007). According to Fil'kin's overview of ancient Chinese and Korean books (Fil'kin, 1952), although numerous indications of Schizandra are mentioned, only plants with black berries growing in the northern regions of China possessed curative properties, whilst the southern varieties with red berries were not considered to be effective.

2.2. Traditional uses in Russia

The great interest in Limonnik (*Schisandra chinensis*) in Russia arises from results of ethnopharmacological investigations of Russian scientists in the Far East regions where the berries and seeds were used by Nanai (Goldes or Samagir) hunters to improve night vision, as a tonic and to reduce hunger, thirst and exhaustion since "it gives forces to follow a sable all the day without food" (Fig. 4; Kokhanova et al., 1950; Fil'kin, 1952; Zemlinskij, 1958). It is of interest to note that these properties of Limonnik were of considerable value to Soviet soldiers during the Second World War, and this may have been the reason for the issue of the official order that led to the initiation of extensive studies of the plant.

The Nanai (нани in their own language, which translates to "nani"; in Russian the name is нанайцы, which translates to "nanaitsy") are a Tungusic people of the Far East, who have traditionally lived along the Heilongjiang (Amur), Songhuajiang (Sunggari) and Ussuri rivers in the Middle Amur Basin. The ancestors of the Nanais were the Jurchens of northernmost Manchuria, and they are closely related to the Ulch, the Oroks and the Oroch, who all consider themselves to be part of the larger Nani group. Historically, by the mid 19th century, the Nanai were caught between Chinese and Russian expansion and suffered pressure from both sides to assimilate the prevailing culture. North of the Sino-Russian border, immigration of ethnic Russians and Ukrainians was on such a scale that by 1915 the Nanai were outnumbered more than 100–1. Currently only 48.5% (5760 individuals) of the ethnic Nanai population of 11,877 in Russia, speak the Nanai/Hezhe language (which belongs to the Manchu-Tungusic branch of the Altai languages: Fig. 2), and only 40 out of 4245 in the ethnic group in China (1990 census) can speak the mother tongue. In Russia, the Nanai currently inhabit the lower Amur river basin, Khabarovsky kray, Primorsky kray, and the republic of Sakha (Yakutiya), corresponding to the regions in which *Schisandra chinensis* is distributed (Fig. 2).

2.3. Cultivation, harvesting and collection

Schisandra chinensis is an endemic relic liana of between 0.5 and 25 m in size (Kozo-Polyanskij, 1946). The leaves, berries and seeds (usually one per berry) are used for commercial and medicinal purposes and are typically harvested from non-cultivated sources (Fig. 5). Although the yield of fruit fluctuates over a 2-year cycle, an average harvest would be in the region of 200 kg/ha from a typical forest, with high density woods producing up to 1700 kg/ha. In the far eastern area of Russia the taiga forest, in which *Schisandra chinensis* is to be found, covers some 6500 ha of which between 1800 and 2000 ha are occupied predominantly by trees of this species. The total annual yield of fruit from this region alone amounts to *ca.* 800 metric tons. Berries are collected by rounds-men at the rate of *ca.* 30–40 kg of berries in an 8 h working day (Gutnikova, 1951). The yield of berries per tree ranges from 0.2 kg for a small tree up to 3–8 kg for large and giant trees.

The cultivation of *Schisandra chinensis* is mainly vegetative and, very rarely, from seed (Titlyanov and Konechnaya, 1963). Plants require conditions of moderate humidity and light, together with a wet, humus-rich soil. The species is not resistant to dry environments or to high levels of moisture. Typically, *Schisandra chinensis* exhibits the best growth alongside river banks at altitudes of up to 250 m above sea level, although cultivation is possible at 500–600 m (Gutnikova, 1951; Agejenko and Komissarenko, 1960). The number, size and resistance to disease of the berries, and consequently the yield of the harvest, strongly increase following cross-pollination (e.g. by *Schisandra*-trained bees) (Shilova, 1963). The typical yield of fruit that may be collected between September and November from cultivated plants is around 2 kg/tree.

The quality of berries and seeds of *Schisandra chinensis* is determined according to GOST-3857-47 and 5241-50, respectively (Zemlinskij, 1958), or according to the National Pharmacopoeia of the USSR (1968a,b, 1990). Typically, 1000 berries (fresh weight 447 g; dry weight 70 g) will yield between 6.2 and 8.7% by weight of

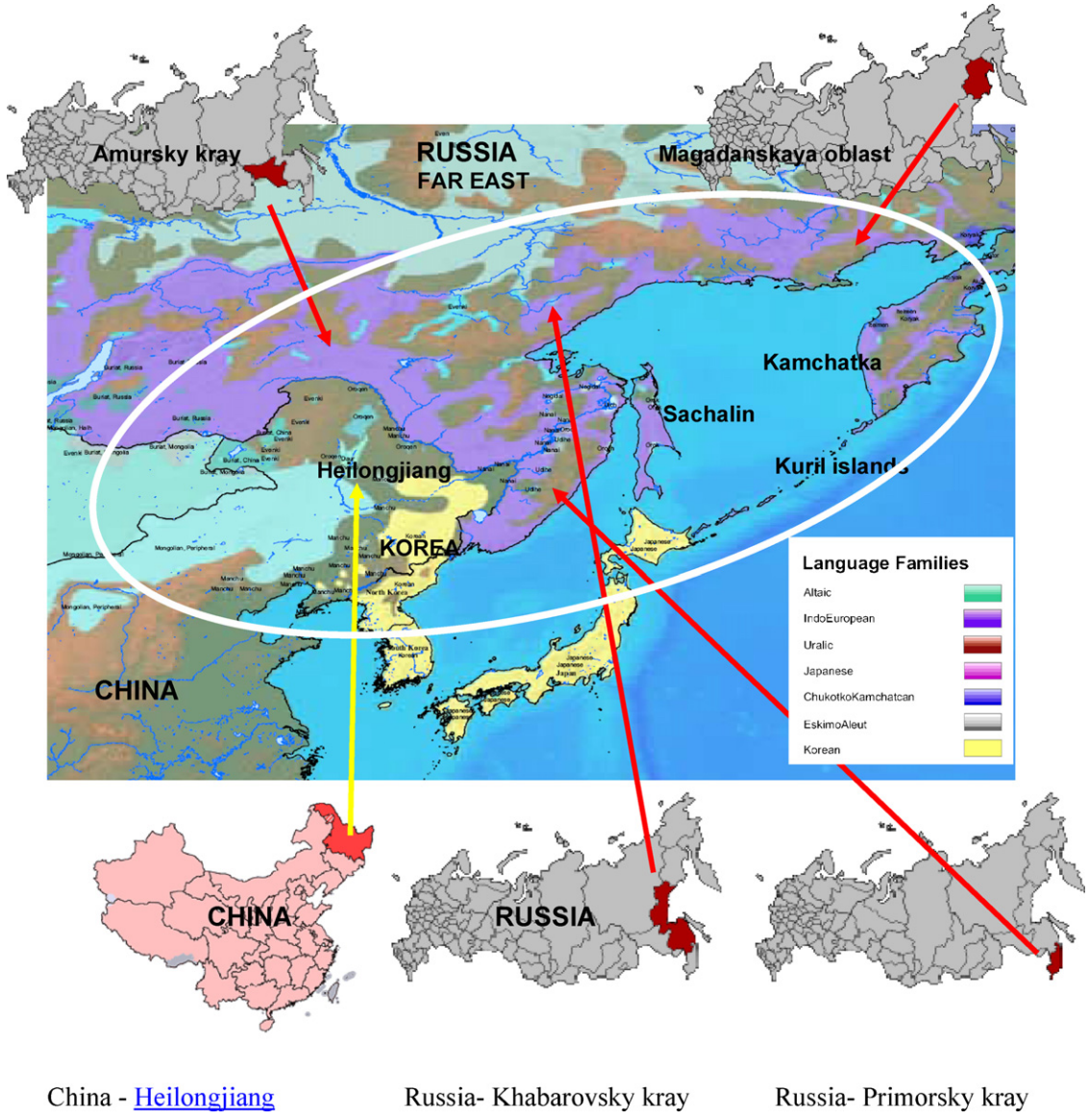

Fig. 2. Regions of the Far East of Russia, South of China and Korea to which *Schisandra chinensis* is native. This ethnographic map also shows the language families associated with this area.

seeds (1000 seeds weighing in the region of 20–25 g) (Gutnikova, 1951; Borozenets, 1958; Agejenko and Komissarenko, 1960). Tens of tons of berries are used annually in the Primorsky and Khabarovsky regions for the commercial manufacture of juices, wines and sweets (Gutnikova, 1951). In the pharmaceutical factories on the Sachalin islands, some 1000 kg of berries are processed per year in the production of tincture of Schizandra. The freshly collected berries are dried at 60–70 °C for 3–4 days with an attendant weight loss of *ca.* 80%. About 60% of the collected seeds are empty and are separated by sedimentation of the dry seeds in water for 24 h. In the preparation of the commercial tincture, 20 kg of dried seeds are extracted with 90 kg of 90% ethanol for 10 days at room temperature (Gutnikova, 1951; Agejenko and Komissarenko, 1960).

2.4. Chemical studies

The first attempts to establish the nature of the active principles responsible for the tonic-related activities of the fruits of *Schisandra chinensis* were focussed on the fatty oil (Balandin, 1940), the organic acids (Pereslegin, 1944a; Varlakov, 1944), and the ether oil. Phytochemical analyses of 40 different formulations, including some 210 infusions, decoctions, tinctures, extracts, etc. prepared from different parts of Schizandra, showed the absence of alkaloids, saponins and vitamins A, B, and D, and the presence of ether oils (0.2–2.33%), resins (0.2%), trace amounts of vitamin C, tannins and staining materials, and large amounts of lipid soluble compounds (24–38%) (Senov, 1952; Tikhonova, 1957). Whilst the seeds were shown to be relatively rich (1.65%) in ether oil compared with the berries (0.3%), the latter were highly acidic (total acidity of 8.51%, which is much higher than that of lemon at 5.83%) and contained large quantities of citric (11%), malic (8%) and tartaric acids (Pereslegin, 1944a; Varlakov, 1944), together with the microelements Cu, Mn, Ni, Zn, Mo, Ti, Ag and Pb (Borozenets, 1958). An artificial mixture containing citric, malic and tartaric acids in a ratio of 70:27:3 was shown to induce, in experimental animals, effects on respiration, arterial blood pressure and heart contractions that were almost identical to those produced by an equivalent dose of Schizandra tincture (ST) (Pereslegin, 1944b).

The non-polar lipid components isolated by extraction with diethyl ether or petroleum ether from seeds of *Schisandra chinen-*

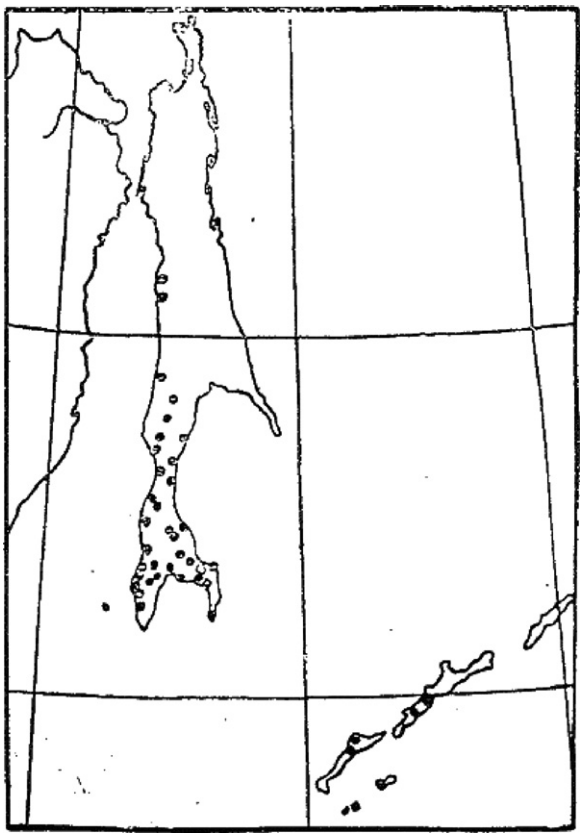

Fig. 3. Geographical distribution of *Schisandra chinensis* on Saschalin and Kurili islands (Agejenko and Komissarenko, 1960).

Fig. 5. Habitat of *Schisandra chinensis*.

sis were initially characterised as a mixture containing 84–94% of the polyunsaturated fatty acids, α-linoleic, β-linolic and oleinic acids (Balandin, 1940). Whilst preparations of these extracts were unstable, it was demonstrated some three decades later that they possessed the ability to increase the spinal reflexes of frogs (Lebedev, 1967). Detailed studies of the ether oil showed that it did not contain aromatic or sesquiterpene hydrocarbons, aldehydes or ketones, and that its physicochemical constants depended on a whole variety of factors (Zapotylko, 1955; Scherbakova, 1965).

The active principle schizandrin was first isolated from the ether oil, obtained from seeds of *Schisandra chinensis,* in a stable crystalline form by Balandin (1951). Seeds were extracted with cold petroleum ether, the solvent removed by evaporation, and

Fig. 4. The Nanai hunter Dersu Uzala who introduced the Schisandra berry to the Russian explorer Vladimir Arsenyev during his expedition to the Usury basin in 1902–1907. Arsenyav was the first to describe numerous species of Siberian flora.

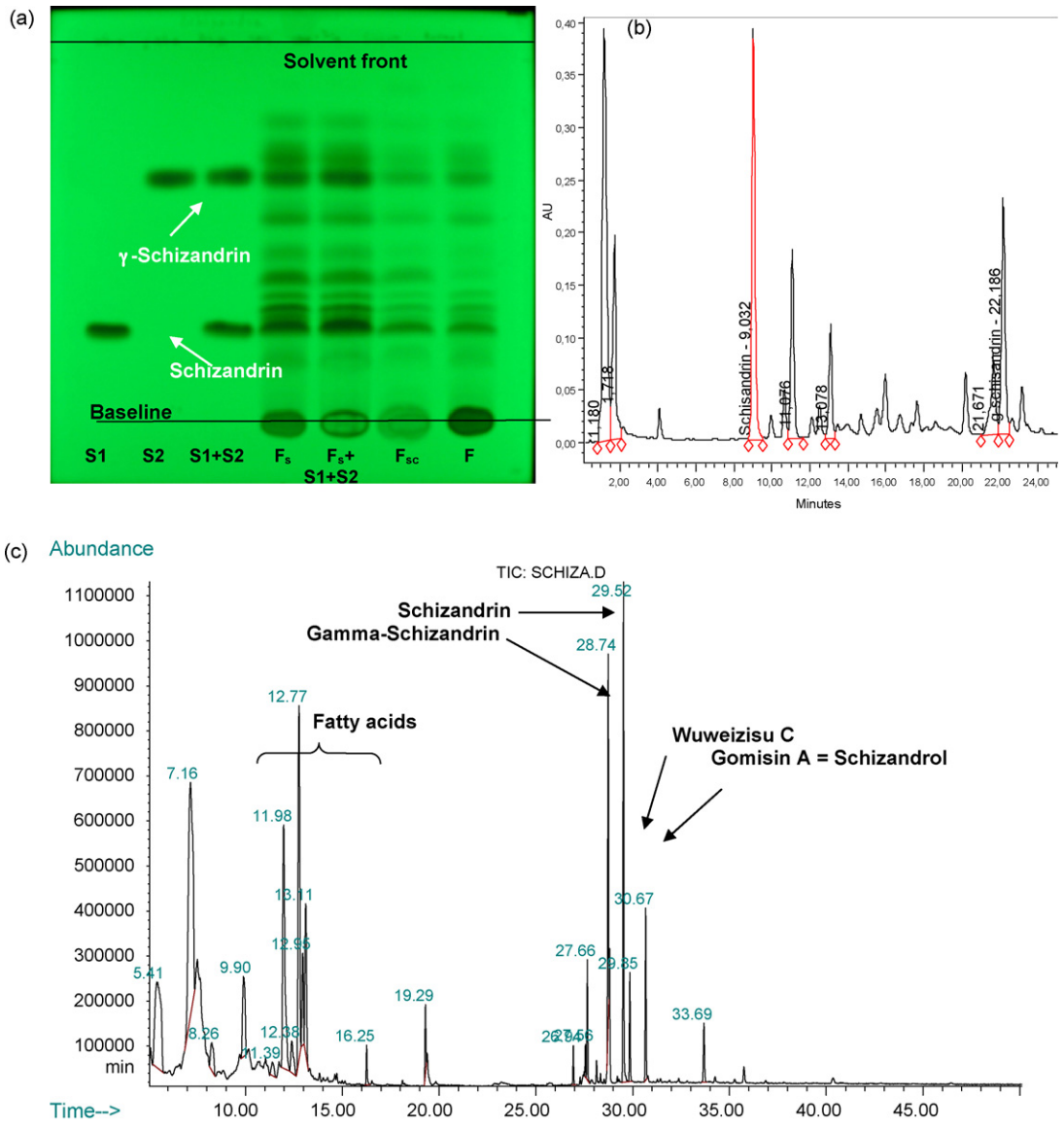

Fig. 6. (a) TLC of schizandrin (S1), γ-schizandrin (S2), schizandrin and γ-schizandrin (S1 + S2), Fructus Schizandrae spissum (F_s), Fructus Schizandrae spissum spiked with schizandrin and γ-schizandrin (F_s + S1 + S2), Fructus Schizandrae siccum (F_{sc}), and Fructus Schizandrae crude drug (F) detected with anisaldehyde reagent and viewed under UV light at 254 nm, (b) RP HPLC of Fructus Schisandrae with detection at 210 nm, and (c) GC–MS of Fructus Schisandrae with MS at 70 eV.

the residue re-extracted with cold ethanol. The ethanolic solution was diluted with water to precipitate insoluble material, and the supernatant treated consecutively with lead tetra-acetate, hydrogen sulphide and carbon dioxide to yield, on evaporation of the final solution, a crystalline precipitate of schizandrin (melting point 129 °C; overall yield 0.12%) (Balandin, 1951). Further studies demonstrated that, among six different fractions isolated from the seeds of *Schisandra chinensis*, schizandrin was indeed the main active principle associated with the increase in mental performance (working accuracy) of healthy subjects (Lebedev, 1951a,b, 1967). Initially, this biologically active compound was reported to possess two aromatic rings and, incorrectly, five methoxy groups to give a chemical formula of $C_{23}H_{32}O_6$ (Balandin, 1951; Lebedev, 1951a,b). Later studies revealed the chemical structure of schizandrin to be 5,6,7,8-tetrahydro-1,2,3,10,11,12-hexamethoxy-6,7-dimethyldibenzo[*a*,*c*]cycloocten-6-ol ($C_{24}H_{32}O_7$; relative molecular mass 432.513) (Kochetkov et al., 1962a,b, 1964). The structure of schizandrin was confirmed by the total chemical synthesis of deoxyschizandrin (Kochetkov et al., 1962c), a minor lignan isolated from the fruit of *Schisandra chinensis* (Kochetkov et al., 1964). In addition to schizandrin, and gamma-schizandrin (Kochetkov et al., 1962a,b,c, 1964), which are the main lignans of the Schizandra berry extract (Fig. 6) and comprise, respectively, 0.5 and 0.3% of the crude drug, a number of other structurally related lignans (Buckingham, 1993), including the gomisins A, B, C, D, E and F (Ikeya et al., 1979a,b) have been isolated from Fructus Schisandrae. Most recently, new groups of nortriterpenoids, including pre-schsanartanin and schindilactones A–C (Huang et al., 2007a), schintrilactones A and B (Huang et al., 2007b), and wuweizidilactones A–F (Huang et al., 2007c), have been isolated from leaves and stems of *Schisandra chinensis* and chemically characterised (Fig. 7).

Several spectrophotometric methods for the quantitative determination of schizandrin and related lignans in plant material have been described (Samoilenko and Saprunov, 1974; Vigorov and Novoselova, 1974; Saprunov and Samoilenko, 1975), these being

based essentially on the assay of thin layer chromatographic (TLC) or column chromatographic fractions pre-treated with concentrated sulphuric acid. Following the application of such methods, the total contents of schizandrin and schizandrol/gomisin A in seed powder of Schizandra and a tincture thereof were reported to be 3 and 0.3%, respectively (Saprunov and Samoilenko, 1975). Additionally, the total content of lignans in the stem and rhizome bark of *Schisandra chinensis* was estimated to attain a maximum value at flowering of 6–11%, whilst the content of schizandrin and schizandrol/gomisin A was determined to be 3–8% (Saprunov and Samoilenko, 1975). More recently high-performance liquid chromatographic (HPLC) methods for the analysis of schizandrin in plant extracts (Wagner et al., 1996), tablets, blood plasma and saliva (Xu et al., 2005) have been developed, and a reversed-phase HPLC method for the simultaneous determination of four lignans in Schizandra herb has been fully validated (Halstead et al., 2007).

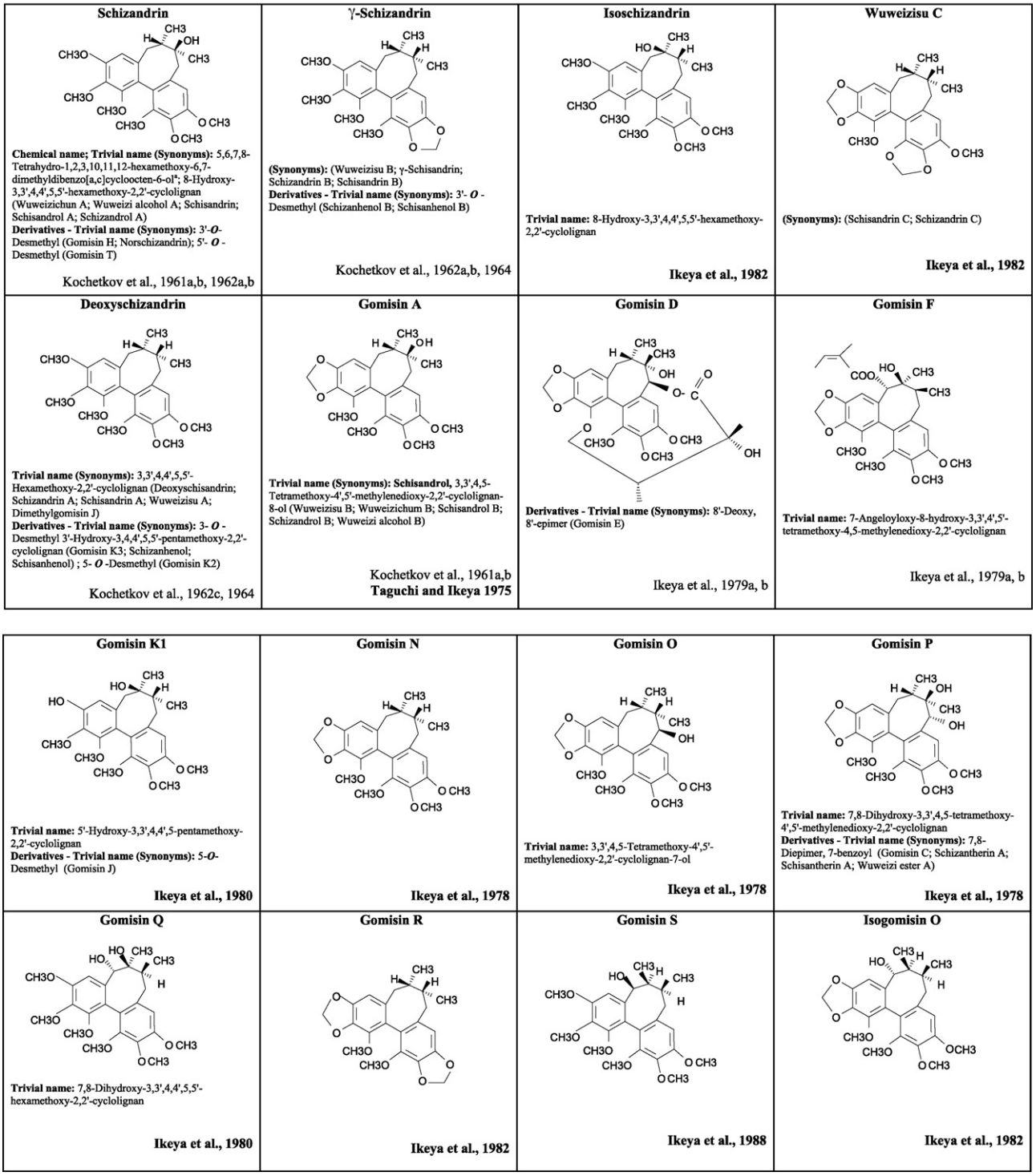

Fig. 7. Chemical structures of compounds isolated from *Schisandra chinensis*. [a]Nomenclature according to 9 CI (Kochetkov et al., 1961a,b; Taguchi and Ikeya, 1975; Ikeya et al., 1978, 1980a,b, 1982a,b,c, 1988).

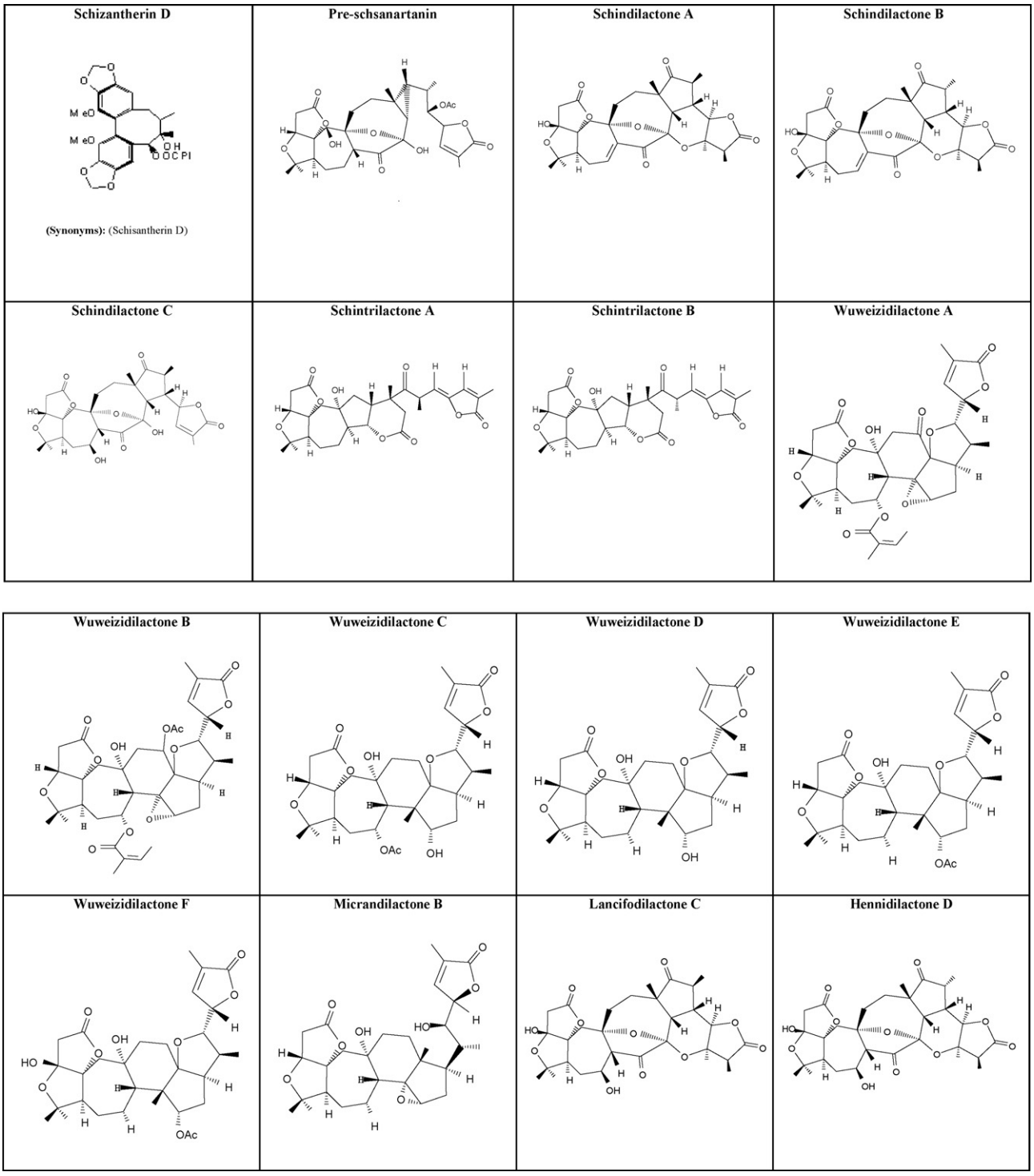

Fig. 7. (*Continued*).

Additionally, a gas chromatography–mass spectrometric method for the determination of schizandrin in human plasma is available for application in pharmacokinetic studies (Ono, 1995).

2.5. Preparations of Schizandra and dosage levels

Examples of Schizandra preparations used in official medicine in USSR/Russia are: (i) Tinctura Fructum Schizandrae, prepared using air-dried fruits and 95% ethanol (1:6, w/v) and administered at a dose of 20–30 drops twice per day (Turova, 1974; Turova and Sapozhnikova, 1982); (ii) Tinctura Seminum Schizandrae, prepared using dried seeds and 95% ethanol (1:5, w/v) and administered at a dose of 20–30 drops twice per day (National Pharmacopoeia of the USSR, 1990 or FS-42-1822-90); (iii) Infusion Fructum Schizandrae (National Pharmacopoeia of the USSR, 1968a,b or GOST-3857-47), prepared using air-dried fruits and water (1:20, w/v) and administered at a dose of 150 mL twice per day (Turova, 1974; Turova and Sapozhnikova, 1982); (iv) Fructum Schizandrae, air-dried fruits

administered at a dose of 0.5–1.5 g twice per day (Turova, 1974; Turova and Sapozhnikova, 1982); (v) Schizandra seed powder (SSP; National Pharmacopoeia of the USSR, 1990 or GOST-5241-50), administered at a dose of 0.5–1.5 g twice per day, before lunch and evening meal, over a period of 20–30 days (although the effects attain their optimal level within 3–7 days) (Lupandin, 1989a); and (v) Schizandra seed extract (SSE), prepared by extracting air-dried seeds with 95% ethanol (1:1, w/v) and administered in a single dose of 0.05 or 0.2 mL/kg (Lupandin, 1965). It should be noted that tinctures are not normally standardised for their content of active lignans and that authenticity assays do not typically include determination of the lignans present.

3. Pharmacological studies on animals

The main pharmacological effects of *Schisandra chinensis* on animals and *in vitro* studies are briefly summarised in Tables 2 and 3.

3.1. Effect on physical working capacity

3.1.1. Dynamic physical load: swimming test

Administration of SSE (produced by Khabarovsk Chemical-Pharmaceutical Factory, Russia) in a dose of 0.05 mL/kg (0.2 mL/kg) extended the duration of swimming of white mice from 71 ± 4 min up to 120 ± 11 min (Lupandin, 1965; Lupandin and Lapajev, 1981; Lupandin et al., 1986), representing an increase of 69%. Following cessation of medication for 24–48 h, animals that had been treated over a 2- or 4-week period with SSE at a dose of 0.5 mL/kg exhibited increased swimming capacities of between 39 and 67%. Moreover, a measurable (but statistically insignificant) increase in the duration of swimming was observed up to 72 h after the termination of the medication. The effect of SSE on the working capacity of rats was almost constant during the first 2–5 h following administration (Ovsyanikova, 1970; Lupandin and Lapajev, 1981).

3.1.2. Static physical load: holding onto rod test

A preparation containing the total lignans of Schizandra, applied in a dose of between 1 and 10 mg/kg, increased resistance to fatigue and to the depriving effect of hexenal in rats subjected to a static physical load as determined by their ability to hold onto a vertical rod (Lupandin, 1989a).

3.2. Anti-stress effects

The application of various damaging conditions, such as cold, heat, noise, chemicals, immobilisation, etc., induces "non-specific" generalised physiological responses that are characteristic of stress, i.e. ulceration of the stomach and colon, increase in adrenal weight, and atrophy of immune system tissue, particularly of the thymus. In the general case, SSE applied in a dose of 0.2 mL/kg has been shown to reduce considerably the 24 h stress-induced and adrenocorticotrophic hormone (ACTH)-induced increase in adrenal weight, and the 48 h stress-induced decrease in adrenal, thymus and body weights, ulceration and haemorrhages of the gastric mucosa (Lupandin and Lapajev, 1981; Barnaulov and Shanin, 1991). More specifically, Schizandra preparations (at dose levels outlined earlier unless otherwise stated) have been demonstrated to increase the resistance of laboratory animals subjected to various stress factors using a number of model systems as shown below.

3.2.1. Heat stress

SSE increased the thermal threshold of mice subjected to overheating in a thermal chamber: untreated mice died when their body temperature rose to 42.5 °C, whilst animals treated with SSE were able to withstand a larger increase in body temperature and succumbed only at 43.8 °C (Lupandin, 1967a; Lupandin and Lapajev, 1981).

3.2.2. Increased oxygen pressure

The survival rate of mice maintained under an oxygen pressure of 4 kg/cm^2 for 2–3 h was significantly higher in a group of animals pre-treated with SSE (73%) than in the control group (27%) (Konstantinov, 1955; Belonosov et al., 1958). Moreover, the decrease in oxygen consumption in the liver and brain of mice under hyperbaric oxygen conditions was lower in the group of animals that had been pre-treated with SSE (Konstantinov, 1955).

3.2.3. Decreased atmospheric pressure

Mice that had been pre-treated with SSE were able to swim for 122 ± 12 min under normal atmospheric pressure and for 70 ± 6 min under low-pressure conditions. In contrast, untreated mice could only sustain 71 ± 4 min of swimming at normal pressure and just 26 ± 2 min at low pressure. These results suggest that whereas SSE did not increase the working capacity of mice under stress conditions, it did have the effect of maintaining capacity at the normal non-stressed level (Lupandin and Fruentov, 1968; Fruentov and Lupandin, 1976; Lupandin and Ovsyanikova, 1986). Treatment of mice with SSE, either alone or in combination with cortisone, increased their resistance to hypoxic and haemic hypoxia but did not alter their resistance to hypercapnia (Lupandin, 1965; Lupandin and Lapajev, 1981).

3.2.4. Cold stress

Administration of SSE to mice immediately following an initial cold stress (swimming for 10 min in water at 12 °C) increased their duration of swim to total exhaustion in water at 30 °C when assayed 3 h after the preliminary stress, in comparison with control mice who had received the cold stress but no medication (Lupandin and Lapajev, 1981). Interestingly, doses in the range 1–10 mg/kg were not active in the test, and higher doses (100 mg/kg) had a negative effect (Lebedev and Kamilov, 1966). Moreover, application of a normal dose of SSE 2 or 1 h prior to the stress decreased the resistance of animals to fatigue. In these experiments, SSE prevented the development of hypertrophy, and later atrophy, of the adrenal glands under acute stress by reducing the symptoms of the general adaptation syndrome (Lupandin and Lapajev, 1981).

When frostbite was artificially induced in limbs of mice through irrigation with a stream of ethyl chloride, the degree of oedema was significantly lower in a group of animals that had been treated with SSE than in a control group (Lupandin and Ovsyanikova, 1986). This effect appears to be associated with the anti-hypoxic effect of Schizandra, since frostbite is known to be a consequence of local oxygen insufficiency in the tissue.

The stimulation of DNA synthesis and mitotic activity in corneal and tongue epithelia following prolonged cold stress is regarded as a compensatory defence response aimed at normalising the disturbance in tissue homeostasis induced by the death of stressed cells. When the body temperature of white rats was reduced to 28–30 °C for 1.5 h per day over a 28-day period, pathological mitosis, mitotic index, and the labelled nucleus index and intensity (measured autoradiographically following the incorporation of ^{3}H-tymidine) in cornea and tongue preparations were all increased compared with those in tissue of control animals (Melnik et al., 1984). Effects of a similar magnitude were also observed following oral administration of SSE (1.9% aqueous ethanol solution in a dose of 5 mL/kg), demonstrating that Schizandra lignans stimulate cell division. However, compared with control animals, no increase in DNA synthesis was detected

Table 2
Summary of the pharmacological activities of *Schisandra chinensis*

Body system	Regulatory system: stress-system	Pharmacological effect: adaptogenic effect
Cardiovascular system	Central and vegetative nervous system	Stimulating effect
Gastrointestinal system	Endocrine system	Stress-mimetic and stress-protective effect
Respiratory system	Immune system	Stress-protective effect

in a group of rats that had been pre-treated with SSE and then exposed to chronic cold stress. The capacity of Schizandra lignans to prevent the cold stress-induced increase of DNA synthesis in the corneal epithelium is regarded as a cellular manifestation of the stress damaging effect of SSE (Melnik et al., 1984).

From the above studies it may be concluded that the adaptogenic effect of Schizandra depends on a number of factors such as the state of the organism, environment, dose, time of application, and the nature of the applied stress.

3.2.5. Liver detoxifying activity: effect on the duration of hexenal-induced sleep and on the working capacity of adrenalectomised mice

Administration of SSE (in a dose of 0.5 mL/kg) to mice over a 2–4 week period decreased the duration of metindal-induced sleep when measured 24 and 48 h after medication had ceased, but the effect was statistically insignificant 6 weeks after drug administration (Ovsyanikova, 1970). Additionally, the non-saponifiable fraction of Schizandra seed oil, which also contains schizandrin, decreased significantly the duration of hexenal-induced sleep when administered to mice in a dose of 20 mg/kg (Ovsyanikova and Lupandin, 1972). Since this effect was potentiated by cocaine, but not affected by the presence of other adrenomimetics such as iprazide, octadine, ornid, and dihydroergotamine, it was suggested that the mechanism of action of Schizandra is associated with excitation of the adrenergic system (Ovsyanikova and Lupandin, 1972). In adrenalectomised animals, the stimulatory activity of Schizandra preparations are either not observed or are distorted. Thus, in adrenalectomised mice, the non-saponifiable fraction of Schizandra seed oil significantly increased the duration of hexenal-induced sleep and decreased working capacity as measured by the swimming test (Lupandin and Lapajev, 1981).

3.2.6. Antioxidant activity

It has been demonstrated that per oral administration of Fructus Schizandrae (in a dose of 1.6 g/kg) strongly increased the content of reduced ascorbate in the blood of rabbits (Nazarova and Kononova, 1958). Similar increases in reduced ascorbate levels may also be observed following administration of extracts of Ginseng and epinephrine, and this appears to be the basis of the antioxidant activities of these drugs.

3.2.7. Recent studies

The stress-protective effects, both *in vitro* and *in vivo*, of Schizandra extract and the lignans from *Schisandra chinensis* have been confirmed in recent publications (Chiu and Ko, 2004; Kim et al., 2004; You et al., 2006; Lee et al., 2007; Panossian et al., 2007). Thus, SSE protects against adriamycin-induced cardiotoxicity in rats (You et al., 2006), while dibenzocyclooctadiene lignans protect primary cultures of rat cortical cells from glutamate-induced toxicity (Kim et al., 2004). The anti-stress effects of the fruit of *Schisandra chinensis* have been confirmed by Lee et al. (2007) in a study in which the activity of an extract was evaluated using a mouse acute stress model. Mice were treated with herbal extract for 7 days before being exposed to stress, in the form of immobilisation and electric shocks to the feet, over a 5-day period. The reduced locomotor activity and the percentage of time spent in the open arms of an elevated plus-maze under stress were recovered by treatment with the extract. Moreover, treatment with *Schisandra chinensis* significantly reduced serum corticosterone levels and prevented stress-induced reduction in spleen size and serum interleukin-2 (IL-2) levels. Taken together, these results suggest that *Schisandra chinensis* could be used to treat stress disorders, in part, by preventing alterations in corticosterone and IL-2 levels.

Another mechanism of action of *Schisandra chinensis* is associated with the induction of the molecular chaperons Hsp25 and Hsp70. Thus, pre-treatment with schizandrin B (1.2 mmol/kg)

Table 3
Summary of the main pharmacological effects of *Schisandra chinensis* on experimental animals

Effects of Schizandra	References
Stress-protective effect: decreases damaging effects of various harmful conditions, including antioxidant, neuroprotective, hapatoprotective, cardioprotective, and gastro-protective activities; prevention of cholesterol- and methyl thiouracil-induced atherosclerosis	Amitina and Vodianova (1958); Barnaulov and Shanin (1991); Belonosov et al. (1958); Chiu and Ko (2004); Egashira et al. (2008); Fruentov and Lupandin (1976); Hung et al. (2007); Ip et al. (1995, 1996); Ivanov et al. (1958); Kim et al. (2004, 2006); Konstantinov (1955); Kuznetsova (1958); Kwon et al. (1999); Lapajev (1967a,b, 1978); Lebedev (1967); Lebedev and Kamilov (1966); Lee et al. (2007); Li et al. (1996, 1997); Liu et al. (1992); Liu and Lesca (1982a,b); Lu and Liu (1991, 1992); Lupandin (1965, 1967a,b,c,d,e); Lupandin and Fruentov (1968); Lupandin and Lapajev (1981); Lupandin and Ovsyanikova (1986); McCord (1988); Melnik et al. (1984); Mikushkin (1961a,b); Panossian et al. (2007); Petkov (1956); Volicer et al. (1966a,b); Volynskij and Mikushkin (1960); Xue et al. (1992); You et al. (2006)
Stimulating effect: increases physical working capacity	Lupandin (1965, 1989a,b); Lupandin et al. (1986); Lupandin and Lapajev (1981); Ovsyanikova (1970)
Stimulation of CNS	Kuznetsova (1958); Lazarev (1946); Lebedev (1951a,b); Lupandin and Lapajev (1981); Pozdnyakov (1945); Sorokhtin and Minut-Sorokhtina (1958); Voevodina et al. (1952); Volicer et al. (1965, 1966a,b); Yefimova et al. (1954, 1955); Zhestyanikov (1945)
Vasodilatory and blood pressure reducing effects	Drake (1942, 1949); Lupandin and Lapajev (1981); Moroz (1956); Pereslegin (1944a,b); Semenov (1948); Sivertsev (1946)
Anti-inflammatory activity, including antioxidant activity, inhibition of arachidonic acid release and biosynthesis of leukotriene B4 in macrophages and	Belonosov and Konstantinov (1959); Ip et al. (1995, 1996); Jung et al. (1997); Liu et al. (1992); Liu and Lesca (1982a,b); Lu and Liu (1991, 1992); Lupandin (1967a,b,c,d,e, 1991, 1992); Lupandin and Maryanovskiy (1972); Lupandin et al. (1986); Ohkura et al. (1990); Tolokneva (1967); Udovenko (1965)
PAF antagonism	Wang et al. (1994); Yevteyeva and Ivina (1958)
Anti-tumour activity	Yasukawa et al. (1992)

produced time-dependent increases in the expression of Hsp25 and Hsp70 in rat hearts, with the maximum enhancement being observable at 48 and 72 h post-dosing, respectively. Heat shock treatment could increase myocardial Hsp25 and Hsp70 expression and protect against ischemia–reperfusion injury (Chiu and Ko, 2004).

The involvement of other mediators of stress response in the adaptogenic effect of Schizandra has recently been demonstrated (Panossian et al., 2007). Thus, daily oral administration of *Schisandra chinensis* over a 7-day period reduced the stress-induced increases in the levels of cortisol, nitric oxide and phosphorylated stress-activated protein kinase (SAPK/p-JNK) in the blood of rabbits immobilised for 2 h. It was suggested that the inhibitory effects of *Schisandra chinensis* on p-SAPK/p-JNK activation may be associated with the anti-depressant activity of the drug as well as its positive effects on mental performance under stress.

3.3. Effect on the central nervous system

Preliminary experiments with frogs indicated that Schizandra is a member of a unique group of stimulators that excite the CNS as a result of a local effect on receptors rather than by direct anti-narcotic action, as is the case for most other CNS stimulants including phenamine and caffeine (Lazarev, 1946). Thus, although an anti-narcotic effect of Schizandra could be observed in experiments in which frog spinal cords were preliminary suppressed by ethanol, the drug was only able to delay, but not prevent, the narcotic effect of the alcohol (Zhestyanikov, 1945; Lazarev, 1946). A similar effect was observed in experiments with rabbits in which the chloral hydrate-suppressed reflex was eliminated by a fatty oil extract of seeds of *Schisandra chinensis* (Kuznetsova, 1958).

Schizandra preparations have been found to exert significant effects on the processes of excitation and inhibition in the spinal cords and higher brain structures of a variety of experimental animals. Thus, the latent period of reflex was decreased by Schizandra in frogs (Pozdnyakov, 1945; Zhestyanikov, 1945; Lazarev, 1946; Lebedev, 1951a; Kuznetsova, 1958), rabbits (Voevodina et al., 1952; Kuznetsova, 1958; Lupandin and Lapajev, 1981) and dogs (Yefimova et al., 1954, 1955). Furthermore, the Schizandra-induced relative decrease in the reflective activity of the spinal cord of frogs was more prolonged than the excitation induced by other chemicals (Zhestyanikov, 1945). Schizandra preparations have been reported to: (i) increase the spinal reflexes and motor activities of those parts of the body innervated by the CNS in dogs (Pozdnyakov, 1945; Lupandin and Lapajev, 1981); (ii) widen the range of assimilation of rhythms by the cerebral cortex (Sorokhtin and Minut-Sorokhtina, 1958); (iii) eliminate the barbamil, chloral hydrate, or aminazine-induced inhibition of bioelectrical activity of the cortex and subcortical structures (Volicer et al., 1966a); (iv) prevent the sodium amytal-induced narcotic effect in rats (Petkov, 1956). In the latter case, the effect of SSE was stronger when administered 0.5 h prior to, rather than together with or following, the application of amytal.

A dose-dependent reversal effect on the conditioned reflexes in dogs has been observed in which Schizandra stimulated nervous activity in low doses but exerted a negative effect at higher doses (Voevodina et al., 1952). The effects on the cholinergic system of the petroleum ether extract of fruits of Schizandra have also been reported to be biphasic (Volicer et al., 1965, 1966a). In small doses the extract decreased the threshold for nicotine convulsions and potentiated the anti-diuretic effect of nicotine and the effect of carbachol on intestinal motility, whilst at higher doses the extract exhibited a cholinolytic effect. In contrast to other psychomimetic substances, Schizandra did not antagonise but actually enhanced the adverse effects of reserpine in mice (namely, catalepsy, lid ptosis, and thiopentone-anaesthesia) (Volicer et al., 1965, 1966a). These results were recently confirmed by Japanese researchers who showed that in mice, schizandrin (at 1 and 10 mg/kg, p.o.) enhanced tremors induced by oxotremorine, a muscarinic M(1) receptor agonist (Egashira et al., 2008).

A number of reports serve to confirm that schizandrin is the main active principle of Schizandra preparations responsible for the effects on the CNS system. Thus, schizandrin has been shown to: (i) stabilise (in a dose of 1 mg/kg) and activate (in doses of 2–3 mg/kg) the bioelectric activity in the cerebral cortex; (ii) recover (in doses of 5–10 mg/kg) chloral hydrate, berbamine or aminazine-suppressed bioelectric activity in the cerebral cortex; (iii) directly excite (in doses of 2–3 mg/kg) the upraised activating system; (iv) increase spinal reflexes in rabbits and decerebrated cats (Lebedev, 1967); (v) inhibit the development of new conditioned reflexes in mice; (vi) enhance the convulsive effects of corazole and strychnine; (vii) extend the duration of hexenal and chloral hydrate-induced sleep in mice (Lebedev and Kamilov, 1966).

In recent studies (Kim et al., 2006; Egashira et al., 2008), schizandrin (1 mg/kg, p.o.) and gomisin A (5 mg/kg, p.o.) were shown to reverse significantly scopolamine-induced cognitive impairments (passive avoidance response and spatial memory) in rodents. Moreover, in *in vitro* studies, gomisin A, C, D and G, and schizandrol B entirely inhibited acetylcholinesterase activity in dose dependent manners with IC_{50} values of 6.71 ± 0.53, 6.55 ± 0.31, 7.84 ± 0.62, 12.57 ± 1.07 and 13.28 ± 1.68 μM, respectively (Kwon et al., 1999; Kim et al., 2006; Hung et al., 2007). These results suggest that Schizandra lignans may be useful in the treatment of cognitive impairment, and that the beneficial effects of the drug are mediated, in part, by enhancement of the cholinergic nervous system.

3.4. Effect on the sympathetic system

A plethora of pharmacological studies of Schizandra have employed the classical approach whereby the mechanism of action of a drug is established from its antagonistic or agonistic interaction with agents the mechanisms of which are already known. Thus, Schizandra preparations were synergistic with strychnine, epinephrine and adrenomimetics (i.e. phenamine, ephedrine, pyridol, etc.), and antagonistic to narcotics (i.e. hexenal, diethyl ether, ethyl alcohol, chloral hydrate, etc.), neuroleptics, sympatholytics, adrenolytics and anti-adrenergic agents (i.e. aminazine, reserpine, dihydroergotamine, darentin, octadion, α-methyl-dihydroxy phenylalanine, etc.) in experiments in which mice and rats were tested using the slipping, swimming or static vertical load tests, or subjected to catalepsy, hypothermia or hyperthermia (Lupandin and Kiyashko, 1970; Lupandin and Lapajev, 1981; Lupandin, 1989a,b, 1991).

3.5. Effect on the endocrine system

The results of numerous studies implicate the involvement of the hypothalamus–pituitary–adrenal (HPA) axis in the effects exerted by Schizandra preparations.

3.5.1. Adrenals and thymus

A decrease in the weight of the adrenals and morphological changes in the adrenal cortex cells were observed in mice treated with Tinctura Schizandrae (in a dose of 0.5 mL/kg) over a 2–4 week period (Ovsyanikova, 1970). However, SSE (in a dose of 0.2 mL/kg) prevented the decrease in weight of the adrenals and thymus of rats exposed to long-term immobilisation stress in the form of hanging by the neck skin fold from a horizontal bracket for 48 h (Lupandin, 1970).

3.5.2. Potentiation of ACTH and epinephrine action on blood eosinophils

Although Schizandra extract exerted no direct effect on the count of eosinophils, the drug potentiated the ACTH and epinephrine-induced decrease of eosinophils in the blood of rats (Lupandin, 1970).

3.5.3. Prevention of testosterone- and hydrocortisone-induced atrophy of adrenals

Enteral administration of a hexane extract of Schizandra seed oil (50 mg/kg) prevented the testosterone- and hydrocortisone-induced atrophy of adrenals in sterilised rats (Volicer et al., 1966b; Lupandin and Lapajev, 1981). No significant changes were observed in the histological structure of the pituitary or of the adrenals, and the duration of the phases of the sex cycles of the animals remained unaltered (Volicer et al., 1966b).

3.5.4. Blood sugar and acid–base balance

The treatment of mice with Schizandra extract gave rise to a decrease in glycogen content in the liver and muscles of up to one-third, and to a *ca.* 1.5-fold increase in glucose level in the liver and blood (Lupandin and Ovsyanikova, 1986). These results indicate that the adaptogen stimulates glycogenolysis and suggest an adrenaline-like effect of Schizandra (Sundejeva, 1950). The findings also explain the increase in blood sugar level (from 76 to 102 mg%; $n = 28$) observed 2 h after administration of 3 g of SSP to healthy subjects, an effect that was even more pronounced when SSP was administered before the morning meal (Sundejeva, 1950). In contrast to other adaptogens, including Ginseng, Echinopanax, Eleutherococcus, Rhodiola, and Leuzea, administration of ST did not decrease glucose levels in mice and rats with experimental alloxan diabetes (Molokovsky et al., 1989).

In a study of the effect of Schizandra on the blood acid–base balance in rabbits, it was observed that the oral intra-parenteral administration of increased concentrations of SSP induced a significant decrease in blood chloride and carbon dioxide levels. This effect was found to be maximal 2.5–3 h after administration of the drug but had disappeared 5 h after treatment. Since the co-administration of SSP with excess sodium bicarbonate exhibited the same effect, it was suggested that Schizandra induces acidosis *via* its action on carbohydrate metabolism, followed by an alteration in lipid and protein metabolism resulting in the formation of products that are directly responsible for acidosis (Plyutach, 1954).

3.6. Effect on the immune system: anti-inflammatory activity

Lung haemorrhages induced in mice following sharp decreases in pressure were remarkably fewer in animals treated with Schizandra compared with a control group (Belonosov and Konstantinov, 1959). In experiments based on Selye's aseptic inflammation test model, it was demonstrated that croton oil-induced haemorrhaged exudation, necrotic leukocyte infiltration and fever could be virtually eliminated in rats by a 7-day pre-treatment with SSE in a dose of 0.2 mL/kg (Belonosov and Konstantinov, 1959). Significant protective effects of SSE were also observed in other models of aseptic inflammation that involved burning the ears of rabbits with water at 56 °C water for 3 min (Lupandin, 1967b), and freezing the hind paws of rats and mice with a stream of ethyl chloride applied for 1 min (Lupandin, 1967c,d). In each case the induced oedemas were far less intense in the Schizandra-treated groups compared with controls, as were the necrotic changes observed in the paws of treated animals assayed 3 h before and 1 h after freezing (Lupandin and Lapajev, 1981). It was suggested that the anti-inflammatory activity of SSE, which is mainly associated with low exudation, is due to an induced increase in the resistance of the capillary vascular wall (Yevteyeva and Ivina, 1958).

A number of experiments on animals have demonstrated that Schizandra preparations can prevent the development of fever induced by the subcutaneous injection of various pyrogenic agents, including milk and Flexner dysenteric bacteria (Udovenko, 1965; Tolokneva, 1967). In rabbits, extracts of Schizandra and Eleutherococcus were shown to exert a synergistic effect in reducing milk-induced leukocytosis and fever (Tolokneva, 1967). Furthermore, the increase in body temperature induced by sulfosin (a 1% sulphur suspension in peach oil) was reduced in guinea pigs when an ethanolic extract of Schizandra (diluted with saline solution; 8 mL/kg) was administered subcutaneously together with, or 1 h after, the pyrogen, and inflammation could be completely prevented by pre-treatment with the adaptogen (Lupandin, 1967e).

3.7. Effect on the gastrointestinal system

The administration of a single dose (1–2 g) of SSP increased gastric secretion, and both free and total acidity in dogs with normal and low acidities, whilst the opposite effect was observed in dogs with hypersecretion and hyperacidity (Ivanov et al., 1958). The normalising effect on gastric secretion commenced during the initial reflex phase, and became maximal during the first 2 days following treatment, before slowly returning to the initial level.

Treatment of rats with SSE reduced reserpine-induced ulceration of the gastric mucosa but was not effective in reducing atopen-induced ulcers (Amitina and Vodianova, 1958; Lapajev, 1967a,b). Stomach ulcers are caused by histamine when the levels of its natural antagonists, the catecholamines, become depleted. Whilst atopen induces histamine release, reserpine induces the release of both histamine and catecholamine. Schizandra lignans, being presumed inhibitors of the enzyme catecholamine-*O*-methyl transferase (the effect of which is to reduce the concentration of catecholamines), prolong the antagonistic effects of the released catecholamines and hence afford protection against the damaging actions of histamine (Lupandin and Lapajev, 1981). Schizandrin, the active principle of SSE, reduced reserpine-induced ulceration when administered at doses of 1 mg/kg, but was not effective at higher doses (2.5 and 12.5 mg/kg) (Lapajev, 1978).

3.8. Effect on the cardiovascular system

3.8.1. Vascular and cardiac action

Tinctures of seeds and berries of Schizandra have been shown to stimulate breathing and reduce blood pressure in rabbits (Moroz, 1956), cats and dogs (intravenous infusion) (Drake, 1942). However, some differential effects of the two tinctures have also been reported. Thus, when applied subcutaneously to mice and frogs at a dose of 0.02 mL/g, a 10% berry tincture led to excitation whilst a 30% seed tincture suppressed the animals and generated a slightly lower blood pressure. Moreover, the seed extract did not affect breathing in rabbits whilst the berry tincture had strong effects in rabbits and cats (Drake, 1949).

Intravenous, but not subcutaneous, administration of Tinctura Fructum Schizandrae (in 20 or 70% ethanol) strongly activated respiration and reduced systemic arterial pressure in rabbits and, to a lesser extent, in dogs. Moreover, the preparation exerted a vasodilatory effect, blocking the peristaltic contractions of isolated intestines of rabbits and strongly suppressing the contractions of isolated hearts of frogs (Pereslegin, 1944a,b). A tincture of Schizandra berries (administered in dilutions of 1:100–1:10,000) was also shown to exert a vasodilatory effect on isolated ears of rabbits, although this effect did not depend on a paralysing action on the

smooth muscles, which showed positive reaction to epinephrine after reperfusion (Semenov, 1948).

A dilute ethanolic extract of Schizandra seeds induced cardiotonic effects on the isolated hearts of frogs (Sivertsev, 1946; Drake, 1949; Lupandin and Lapajev, 1981), whilst intravenous infusion of the extract induced a strong hypotensive effect (reducing the cardiac rhythm and increasing respiration), which disappeared some 3–5 min after administration of the drug (Drake, 1949). Some evidence has been presented that suggests that these effects could be due to the presence of high amounts of citric, malic and tartaric acids in the extract (Pereslegin, 1944b).

In contrast to the above, no significant effects on cardiac rhythm, blood pressure or respiration were observed in response to the intraperitoneal administration of SSE (in a dose of 2 mL/kg) to rabbits (Lupandin and Lapajev, 1981). Similarly, administration of Tinctura Fructum Schizandrae to rabbits over a 3-week period produced no significant effects on blood leukocytes and haemoglobin content (Pereslegin, 1944a; Belikina and Prokofjeva, 1959). On the other hand, long term treatment with SSE (in a dose of 0.2 mL/kg) was reported to increase erythrocytes and total proteins in the blood of mice (Ovsyanikova, 1970), whilst other researchers found that such treatment decreased blood haemoglobin content but did not alter blood proteins (Lapajev, 1978).

3.8.2. Development of experimental atherosclerosis

The prophylactic effect of SSP, administered in doses of 50 and 200 mg/kg, respectively, on the development of experimental atherosclerosis in dogs and rabbits has been reported (Volynskij and Mikushkin, 1960; Mikushkin, 1961a,b). In each case, both the blood cholesterol content and the lecithin/cholesterol ratio were significantly lower in treated animals compared with the control group. In rabbits, SSP prevented the development of cholesterol- and methyl thiouracil-induced atherosclerotic manifestations, including lipoidosis of the aortic and coronary arterial vessels. A similar effect on the incorporation of lipid vesicles in the liver tissue of dogs was also observed. Interestingly, in rabbits, lower doses of SSP (50 mg/kg) were ineffective, whilst higher doses (350 mg/kg) induced the development of atherosclerosis. Moreover, administration of SSP in a dose of 200 mg/kg to hypertensive rabbits failed to exert any effect (Mikushkin, 1961a,b).

3.8.3. Capillary permeability and resistance

Oral administration of ST (in a dose of 0.5 mg/kg) is reported to decrease capillary permeability in rabbits (Belikina and Prokofjeva, 1959). Whilst SSP (in a dose of 2 g/day for a period of 1–5 weeks) increased capillary resistance in 10 out of 14 healthy subjects studied (Yevteyeva and Ivina, 1958), it could not replace vitamin therapy in patients with significantly increased capillary fragility.

3.9. Herb–drug interactions

Although the topic of herb–drug interaction has attracted a great deal of attention recently, the results obtained are sometimes confusing since findings derived from *in vitro* studies cannot necessarily be extrapolated to the whole organism. Thus, *in vitro* studies have shown that Schizandra fruit and shoseiryuto (a herbal preparation containing Schizandra fruit, Ephedra herb and Cinnamon bark) exhibit a strong inhibitory effect on cytochrome P450 3A4 (CYP3A4) (Iwata et al., 2004; Makino et al., 2006). However, whilst the *in vitro* effects of shoseiryuto and grapefruit juice on rat CYP3A4 activity were comparable, shoseiryuto did not significantly alter the plasma concentration profile of nifedipine in rats to the same degree as grapefruit juice (Makino et al., 2006). These results indicate that *in vivo* experiments with extracts of herbal medicines prepared in the same dosage form as would be administered to human patients are absolutely essential in order to provide useful and accurate information about herb–drug interaction.

3.10. Toxicity

The minimal toxic oral dose of SSP in mice is 3.6 g/kg (Semenov, 1948). The alcoholic extract of SSP is reported to be practically non-toxic to mice and dogs, whilst toxic effects of the ethereal oil and the fatty oil derived from Schizandra seeds could only be observed when very high dose levels were administered orally to these experimental animals (Kuznetsova, 1958). The acute toxicity of Schizandrin has been studied in mice following i.p. administration of the drug in the form of a water:ethanolic suspension (ethanol to the level of 3.75 g/kg body weight) at doses in the range 25–1000 mg/kg body weight. Schizandrin exerts no significant effects on blood pressure, breath or motility, but at high doses it induces convulsions (ED_{50} 175 mg/kg), falls to a side position (ED_{50} 77.5 mg/kg) and paresis (ED_{50} = 370 mg/kg). Doses of 500 and 1000 mg/kg were not fatal to experimental animals, however, and recovery was achieved in 24 h. The subchronic toxicity of Schizandrin was studied in rabbits orally administrated a water:ethanolic suspension of the drug in the dose of 10 mg/kg for 30 days. No behavioural changes or effects on body weight or blood morphology were observed, and histological studies of the brain, cardiac muscle, lung, liver, kidneys, stomach and intestine did not reveal any changes (Lebedev, 1951a,b, 1967).

4. Pharmacological studies on isolated organs, cells and enzymes

4.1. Effects on isolated organs and tissues

Tinctures (95% ethanol) of seeds (10%, w/v) and berries (20%, w/v), employed in dilutions of 1:100 or 1:250, reduced the amplitude of cardiac contractions in experiments on isolated frog heart (Drake, 1942; Pereslegin, 1944a; Sivertsev, 1946), inhibited the motility of isolated rabbit intestine (Drake, 1942, 1949; Pereslegin, 1944a; Lupandin and Lapajev, 1981), induced the dilatation of vessels in isolated rabbit ears (Drake, 1942, 1949; Semenov, 1948), and stimulated the contraction of the uterus isolated from cats or rabbits (Drake, 1942). Ethanolic extracts of Schizandra berries harvested in diverse geographical areas were found to stimulate the contraction of isolated frog muscle to different degrees (Georgijev, 1958): thus a 70% extract prepared using Korean berries exhibited a higher activity than a 96% extract from Russian berries. A water extract of the leaves of *Schisandra chinensis,* diluted in the range 1:2500–1:5000, increased the force of the contractions of isolated frog heart (Sivertsev, 1946).

4.2. Effects of gomisin A on arachidonic acid release and biosynthesis of leukotriene B4 in macrophages

Macrophages are involved in the inflammatory response of an organism, and generate various mediators of inflammation, for example cytokines and arachidonic acid metabolites including prostaglandins, leukotrienes and other hydroxy-eicosatetraenoic (HETE) acids (i.e. 5-HETE, 12-HETE and 15-HETE). In isolated macrophages, the production of leukotriene B_4 (LTB4) is inhibited by gomisin A, but this is not due to its effect on arachidonate 5-lipoxygenase (Ohkura et al., 1990). It is believed that gomisin inhibits arachidonic acid release by a mechanism, possibly involving the phospholipase C pathway, which does not affect phospholipase A2. It is suggested that, since LTB4 plays a role in

inflammatory liver diseases, this finding may explain the anti-hepatotoxic effect of gomisin and Schizandra (Ohkura et al., 1990). It should be noted that the inhibition of arachidonic acid release in other cells and tissues that are involved in stress responses may also be important with respect to the adipogenic effects of Schizandra.

4.3. Platelet activating factor receptor antagonistic activity

1-*O*-Alkyl-2-acetyl-*sn*-glycerol 3-phosphocholine (PAF) plays an important role in inflammation, allergy, cardiac anaphylaxis, thrombosis, gastrointestinal ulcerations, vascular permeability, hypotension, endotoxin shock, etc., and is active in nanomolar concentrations. Extracts of Schizandra fruits exhibit PAF receptor antagonistic activities, and the most active constituent was shown, through *in vitro* binding experiments with washed rabbit PAF receptors, to be schizandrin A (Jung et al., 1997). Since this lignan also inhibits PAF-induced human blood platelet aggregation in a dose dependent manner ($IC_{50} \sim 5\ \mu M$), it is postulated that one mechanism for the anti-inflammatory effects of Schizandra is associated with the inhibition of PAF-mediated inflammatory responses (Amroyan E.A. and Aivazyan A.G., 1999; unpublished data).

4.4. Antioxidant activity

Schizandrin (in a dose of 10 mg/kg administered 18 h prior to stress) prevented the cold stress-induced increase in malonic dialdehyde in rat liver homogenate (Lupandin et al., 1986; Lupandin, 1991, 1992), and inhibited non-enzymatic ascorbate-dependent lipid peroxidation in liver homogenate *in vitro* at a concentration of 10 μg/mL (Lupandin and Maryanovskiy, 1972; Lupandin et al., 1986; Lupandin, 1991, 1992). Similar antioxidative effects were also observed in intact rats. It should be stressed that the antioxidant activity of Schizandra lignans play a leading role in the hepatoprotective (Liu and Lesca, 1982a,b; Lu and Liu, 1991, 1992; Liu et al., 1992; Ip et al., 1995, 1996), myocardial protective (McCord, 1988; Li et al., 1996, 1997) anti-tumour (Yasukawa et al., 1992) and anti-inflammatory (Wang et al., 1994) actions of Schizandra preparations. These lignans also exhibit a protective action in oxidative stress-associated disorders such as ageing-related brain ischemia (Xue et al., 1992).

4.5. Stimulation of oxygen consumption, tissue respiration and tolerance to oxygen intoxication

An infusion or a decoction of Schizandra berries stimulated respiration in mice leading to increases in both oxygen consumption (by 33.6%) and carbon dioxide production (Konstantinov, 1956, 1959). When ethanolic tinctures (20%) of Schizandra were administered subcutaneously in doses of 0.1 and 0.3 mL/kg to groups of mice ($n = 30–40$ per group) 2 h before the animals were sacrificed, increased dehydrogenase activities (as assayed by the rate of decolourisation of methylene blue) and decreased reduced glutathione levels were observed in homogenates of isolated liver and brain tissues compared with those of a control group treated only with 20% ethanol. The largest effect was observed in brain tissue, particularly in groups of animals that had been subjected to high oxygen pressure (4 atm) for the 2-h period (Konstantinov, 1956, 1959; Belonosov et al., 1958). Under such conditions, the consumption of oxygen in the tissues decreased sharply, but extracts of Schizandra berries increased the uptake of oxygen and the release of carbon dioxide compared with the control group. In a further set of experiments it was shown that berry extracts exerted a protective effect against oxygen toxicity. Thus, the survival of mice under hyperbaric conditions was strongly increased (73% survival in the treated group compared with 26% in the control group) on the day of administration of the drug, whilst after 4 days under these conditions 20% of the treated mice, but none of the control group, survived (Konstantinov, 1956, 1959; Belonosov et al., 1958). Surprisingly, treatment with SSE led to a decrease in oxygen consumption and carbon dioxide production in mice (Konstantinov, 1956, 1959).

4.6. Stimulation of the carbohydrate–phosphorus metabolism

Two hours after per oral administration of Schizandra oil (5 mL/kg; obtained by ether extraction of seeds or berries) or schizandrin (10 mg/kg), the free sugar level in the blood of groups of rabbits ($n = 10$ per group) was reduced to the lower limit of the normal value (Belonosov and Krasilnikova, 1955). Interestingly, water or ethanol extracts of Schizandra were inactive. However, SSP stimulated glycolysis in the brain, liver and muscles of rabbits ($n = 20$) that had been treated orally with 0.5 g/kg over a 3-day period. When assayed on the 4th day, the levels of fructose diphosphate, phosphoglycerol and lactate were all found to be increased in the isolated tissues derived from the treated groups compared with controls (Belonosov and Makarevich, 1958; Belonosov et al., 1958). The largest increases were of fructose diphosphate in liver tissue and lactic acid in muscle.

Since energy provision is strongly associated with phosphorylation, the effect of Schizandra seed preparations on the activities of enzymes involved in phosphorous metabolism was studied together with the incorporation and accumulation of radio-labelled inorganic phosphorus in various tissues of rabbits and mice (Belonosov, 1957; Belonosov and Makarevich, 1958). Thus, administration a single dose (0.1 mL, s.c.) of an ethanolic tincture (10%) of Schizandra to mice ($n = 10$ in both treated and control groups) increased adenosine triphosphatase and phosphorylase activities in homogenates of isolated muscles within 2 h. Moreover, administration of SSP (0.5 g/kg) led to increases in alkaline phosphatase and glycerophosphatase activities in the blood of rabbits after 2 h. When a group of rabbits ($n = 36$) was treated with the same preparation at the same dose rate, the incorporation of ^{32}P in the kidney, liver and brain increased in 12–120 h following administration, and the ratio of ^{32}P accumulated into the liver compared with the brain decreased from 240 (in the control group) to 138 (Belonosov, 1957; Belonosov and Makarevich, 1958; Belonosov et al., 1958). The absorption of total phosphorus and of P^{32} from the gastrointestinal tract into the blood also increased following administration of SPP. All of these results provide indirect evidence that Schizandra stimulates tissue respiration and energy provision.

5. Studies on healthy human subjects

The main pharmacological effects of *Schisandra chinensis* on humans are briefly summarised in Table 4.

5.1. Physical working capacity

The administration of a single dose (2 mL) of SSE to groups ($n = 8–10$) of male subjects significantly increased their working capacity and physical force by 24–42%, as measured hourly using a Dubua ergograph over a period of 3 h after treatment, compared with the performance achieved prior to treatment (Karo, 1945; Lazarev, 1946; Lupandin and Lapajev, 1981). However, when various Schizandra preparations (including water and 70% ethanol extracts of berries and seeds) were tested, only the seed tinctures were found to be active (Karo, 1945; Lazarev, 1946). An investigation involving 23 student volunteers showed that the stimulation of working capacity in the Dubua test began 2–2.5 h after the uptake of SSP, reached a maximum value (72.4 kg/m *cf.* with 33.4 kg/m

achieved by non-treated controls) at 3.5 h, and disappeared at 5.5 h (Kokhanova et al., 1950). A more pronounced tonic effect was observed in individuals subjected to fatigue (by sawing wood for 5 min with a frequency of 45 movements/min) prior to treatment with SSP: in this case working capacity in the Dubua test increased from 27.5 kg/m in the control group to 77 kg/m in the treated group (Kokhanova et al., 1950). When treatment with SSP (1 g/day) was continued over a long period, however, the stimulatory effect could no longer be observed (Kokhanova et al., 1950; Yefimova et al., 1954) and an interruption in medication of at least 10 days was required in order to restore the tonic effect (Yefimova et al., 1954).

Andrejev and Georgijev (1958) observed a 49.2% increase in working capacity of 19 healthy individuals who had been treated with SSP and then subjected to a classical ergographic procedure. Additionally, the maximum number of rotations of a pedal-powered machine (with a 60 kg loading) that could be accomplished prior to exhaustion by a group ($n = 7$) of healthy subjects increased twofold (*cf.* with control) following administration of a single dose (1 g) of SSP (Yefimova et al., 1954). In the same test, a 1.5 g dose of SSP has been reported to increase the working capacities of groups of students ($n = 41$) from 620 kg/m (mean value recorded with the placebo group) to 1736 kg/m (mean value for the treatment group) (Kokhanova et al., 1950).

In contrast, administration of ST (2 mL) had a negative effect on the performance of runners ($n = 13$) over a sprint distance of 100 m. However, when the same individuals were subjected to an identical treatment and then asked to run a 1000 m course, a positive effect on performance was observed in 60% of the runs ($n = 5$), and the average improvement in run time for all runners was 4.45 s (Astanin et al., 1943). Administration of ethanol or caffeine prior to the 1000 m run resulted in a significant reduction in performance in comparison with the preliminary runs, and the results were remarkably worse after receiving SSP or amphetamine. In this context, schizandrin was reported to be the active principle in SSP since treatment with the isolated compound increased the working capacity of 20-year-old athletes ($n = 129$) running over a distance of 3000 m such that the run time of the treated athletes improved significantly (by 1 min 42 s on average) compared with those of the placebo group (medicated with glucose only) (Lebedev, 1967, 1971a).

When SSP (6 g) or placebo capsules were administered to 45 Red Army soldiers ($n = 23$, treatment group; $n = 22$, placebo group) undertaking a 20 km ski run, a diminution in the shortage of breath and exhaustion, the elimination of the feeling of thirst and dryness in the mouth, and a reduction in muscular pain and the time taken to complete the run were observed in the treated group (Murtazin, 1946). Similar sets of results were recorded for SSP-treated ($n = 28$) and control ($n = 28$) groups of civilian skiers tested under the same conditions.

In a study of the effect of SSP on highly qualified gymnasts, it was established that although initial administrations resulted in a decrease in working capacity and intensity of training, further doses significantly increased these capabilities compared with the initial values (Korolevich and Lupandin, 1967; Lupandin and Lapajev, 1981). Moreover, the level of intensity of training attained during SSP treatment remained the same even after administration of the phytoadaptogen had ceased. Comparable results were obtained when groups of highly qualified athletes (62 oarsmen) and non-trained subjects (58 solders) were treated with SSE (2 g/day). Although physical working capacity (as measured by the PWC_{170} test) was augmented in both groups, the increase in the group of non-trained subjects was observed during the first days of the study whereas in the group of well-trained athletes it was observed only after 7 or more days of drug uptake (Lupandin, 1990a). Similarly, a placebo-controlled study involving the treatment of a group of basketball players ($n = 30$) with SSP (0.5 g/day) revealed that during the first 3 days of drug administration, the coordination of the movements of the trained athletes temporarily decreased, but after 6 days their physical endurance had increased (Levchenko, 1971). Thus, when athletes were given 90 s to cover as much ground as possible followed by throwing the ball from under the ring, the distances run after treatment increased significantly ($p < 0.001$) by 7 and 13.4 m *versus* control in the first and second attempts, respectively. Moreover, the differences in distance covered between the first and second attempts decreased from 6.9 m prior to treatment to 0.5 m following administration of SSP. Apparently, no statistically

Table 4
Summary of the main pharmacological effects of *Schisandra chinensis* on humans

Effects of Schizandra	References
Increases endurance, accuracy of movement and physical working capacity	Andrejev and Georgijev (1958); Astanin et al. (1943); Eglit et al. (1965); Grigorenko and Berdishev (1988); Karo (1945); Kokhanova et al. (1950); Korolevich and Lupandin (1967); Lapajev (1978, 1982); Lebedev (1967, 1971a, b); Levchenko (1971); Lupandin (1990a,b); Yefimov and Vlasova (1945); Yefimova et al. (1954)
Increases endurance and mental performance	Berdyshev (1995); Gubchenko and Fruentov (1981, 1986); Kochmareva (1958); Lebedev (1955, 1967); Lupandin (1990a, b); Narimanian et al. (2005); Negoda et al. (1999); Roslyakova et al. (2000); Vezirishvili et al. (1999)
Stimulation of CNS	Yefimov and Vlasova (1945); Markova and Samoilova (1954)
Improves impaired visual function and vision in darkness	Galochkina (1948); Golovin and Golovina (1963); Lebedev (1971a, b); Minejeva and Svindyukova (1968); Sinovich and Akhmetova (1958); Sosnova et al. (1984); Trusov (1953, 1958a,b)
Local anti-inflammatory effect	Lupandin (1966)
Improves quality of life	Narimanian et al. (2005)
Prevention of chemotherapy-induced immunosuppression in cancer	Kormosh et al. (2006)
Radioprotection	Fedorova et al. (1994)
Gastric hyper- and hypo-secretion, chronic gastritis, stomach and duodenal ulcers	Amitina and Vodianova (1958); Lapajev (1958, 1961, 1967a,b, 1969, 1978); Lapajev and Mosyakova (1970); Lapajev and Sokolova (1970); Masyuk (1949); Surovtseva et al. (1958)
Effective in neurosis	Farutina (1951)
Effective in astheno-depressive syndrome	Galant (1958); Galant et al. (1957); Leman (1952); Romas (1958, 1967); Rossijskij (1952a,b); Sivertsev (1946, 1950); Staritsina (1946); Zakharov (1956)
Effective in influenza treatment	Lebedev (1970a,b, 1971a,b); Shadrin et al. (1986)
Effective in the treatment of pneumonia	Pavlushchenko (1981); Narimanian et al. (2005)
Wound healing effect	Walter (1955, 1956)
Normalization of arterial blood pressure and cardiac rhythm in hypertensive and hypertensive patients	Agejenko and Komissarenko (1960); Gaistruk and Taranovskij (1968); Lebedev (1971a,b); Leman (1952); Lidskij (1959); Lupandin and Lapajev (1981); Masyuk (1949)

significant effect was observed with respect to the accuracy of the throws.

When various doses (2, 5, 10, or 15 g) of Tinctura Seminum Schizandrae (20%) were applied to oarsmen ($n = 22$) and athletes ($n = 6$) at times of 1, 2 or 3 h prior to physical exertion, improvements in the function of the respiratory and cardiovascular systems, increases in hand muscle power (as determined by hand dynamometry after the exercise), decreases in weight loss, and reductions in the times taken to cover the prescribed distances were observed (Eglit et al., 1965). Effects of the treatment were particularly marked in the case of single canoe oarsmen treated with 5–10 g of Schizandra 1 h prior to physical load.

The effect of Schizandra extract (one tablet three times a day) on the working capacity, endurance and adaptation in a group ($n = 18$) of sport divers, an activity comprising high-speed underwater swimming and involving a combination of sub-maximal load with a hypoxia, has been investigated (Lapajev, 1982). Arterial blood pressure, heart rate and spirometric data were recorded both before and after (1 and 30 min) each diver had swum a distance of 100 m in flippers with an intensity of 80–100% of maximum effort. Determination of an integral index of adaptation confirmed that, following treatment, athletes exhibited a higher adaptation of the cardiovascular system to loads compared with control levels.

A single dose of Schizandra tea induced a tonic effect in sailors ($n = 200$) keeping watch at sea (Grigorenko and Berdishev, 1988). Daily administration of the tea remained effective during the first 7–10 days of treatment, but following 2 or 3 weeks of continuous use, some subjects suffered from sleeplessness, excitability and a lowered sense of general well-being. Such negative side effects could be eliminated by substituting black tea for Schizandra tea for a number of days at various intervals within the treatment regime. Uplifting effects of Schizandra have been reported for adolescents working in a factory (Yefimov and Vlasova, 1945), whilst the same dosage of adaptogen produced exactly the opposite effects (i.e. suppressed muscular activity, depression and sleepiness) in subjects labouring in "hot" workshops.

5.2. Accuracy of movement

A special training apparatus was employed to evaluate the quality of a performed standard exercise in terms of total score and the mean number of accurate movements in every exercise (Lapajev, 1978). Whilst a single dose (0.5 mL) of ST administrated 30 min before the test had no effect on the accuracy of movement in individuals aged between 18 and 20 years, a positive outcome was observed following multiple dose administration ($n = 135$). This effect became much stronger when the treatment was continued over a prolonged period (38 days, $n = 65$), but only persisted for 2 days ($n = 68$) when administration of the drug ceased. It appears that the effect on accuracy of movement of a single dose of Schizandra depends on the type of preparation (extracts and seed powder, for example, exert a positive effect), the dose, and the time of administration (Lupandin and Lapajev, 1981). It has also been reported that repeated doses of Schizandra facilitate subjects to develop skills based on accurate movement more readily (Korolevich and Lupandin, 1967; Lapajev, 1978).

5.3. Mental performance and working capacity

In two sets of experiments ($n_1 = 20$, $n_2 = 23$), young (21–24 year old) telegraph-operators were asked to transmit Morse code at maximum speed for a period of 5 min, and the frequency of errors was measured and normalised at 100% (Lebedev, 1955, 1967). Following treatment with a single dose of Schizandra extract (10% in 70% ethanol, 30 mL) or schizandrin (5, 10, or 20 mg), the test was repeated and the error frequency was within the range 84–103%, whilst that of the control group (treated with a placebo of glucose or 70% ethanol) was 130%. It was concluded that Schizandra preparations prevent or reduce exhaustion-related errors in a manner similar to that observed following treatment with Ginseng or phenamine. The effect of the latter, however, is more one of excitation, which leads to increased speed but not performance. By using a test method involving the correction of texts in which fatigue affected the accuracy but not the speed of work, Kochmareva (1958) was able to demonstrate that 38 (65%) of a group of 59 students who had been treated with SSP showed an improvement in performance, and of these 7 presented an increase in the amount of work performed, 14 exhibited an enhancement in the quality of correction, and 17 showed improvements with respect to both of these aspects. Six components isolated from Schizandra were screened for their effect on mental working capacity in a study involving 20 individuals, each of whom was asked to correct texts initially whilst fresh (this error frequency being normalised to 100%) and then repetitively following administration of placebo and each of the analytes separately (Lebedev, 1951a,b, 1967). Schizandrin was found to be the most efficacious in preventing exhaustion-related errors since, when administered at a dose of 3.6 mg, error levels fell to 95% relative to the control, whilst the frequency of errors in the placebo group was estimated at 228%.

A detailed comparative study of the effect of Schizandra and some other adaptogens (Eleutherococcus, Aralia, Echinopanax and saparal) on the functional state of helicopter crew is available (Gubchenko and Fruentov, 1986). The subjects, consisting of 665 pilots, navigators, mechanics and radio-operators, were treated with the preparations or placebo at a dose of 1 mL twice a day for 10 days and were tested before a flight and again 5–15 min later, and finally 1 and 3 h after landing. The psycho-physiological state of each participant was evaluated through the application of seven tests including assessment of dynamic tremometry, sensomotor response, and attention and memory functions. None of the adaptogens tested prevented the decrease in functional state recorded immediately after landing. All were effective, however, in expediting the restoration and elevation of the basal level of the functional state, with Aralia showing the most pronounced activity and Schizandra the least. Similar results were obtained in an extensive study involving 1327 healthy subjects of whom 248 were in the group treated with Schizandra (Gubchenko and Fruentov, 1981).

The effects of an extract of Schizandra on visual memory, dimensional imagination and perception, distribution and switch of attention, sensomotor response on a moving object, arterial blood pressure, frequency of heart contraction, and stability of balance in Romberg's test were evaluated in a placebo-controlled study involving 59 stewardesses (Lupandin, 1990b). Participants were tested before and after long haul (7–9 h) flights and the results revealed that the administration of Schizandra significantly improved all of the assessed parameters, particularly those associated with sensomotor response and Romberg's test, and that the effect was more pronounced in spring compared with autumn.

Professionals who are routinely required to study scientific-technical documentation displayed on computer monitors often complain of visual fatigue, reduced level of attention, slower reactions and a general feeling of tiredness. Negoda et al., 1999 tested sensory fatigue using an ocular light test in which the critical frequency of light flashes (CFLF) was determined at the start and at the end of a working day that had involved 6 h of intense exertion of the eyes. In a control group ($n = 23$), the initial CFLF values were 42.33 ± 0.76 Hz for males and 41.64 ± 0.65 Hz for females, but these reduced to 40.33 ± 0.64 and 39.54 ± 0.57 Hz, respectively, following the work period. A separate group ($n = 21$) of healthy workers were treated for 1 month with Tinctura Seminum Schizandrae at a dose

of 20–25 drops taken orally twice a day, 30 min before meals. In this group the CFLF values at the start of the working day were 41.81 ± 0.78 and 42.00 ± 0.68 Hz for males and females, respectively and, prior to treatment, these had reduced to 40.45 ± 0.77 and 40.00 ± 0.51 Hz ($p < 0.001$) at the end of the work period. After therapy, however, the end-of-day CFLF values were 42.45 ± 0.76 Hz in males and 42.50 ± 0.72 Hz in females, demonstrating that adaptogen treatment significantly ($p < 0.001$) reduced sensory fatigue in computer operators involved in mental activity.

Rodelim, a fixed combination of standardised extracts of *Schisandra chinensis, Eleutherococcus senticosus* Maxim and *Rhodiola rosea* L., has been shown to increase significantly mental working capacity in healthy computer operators ($n = 60$) working night shifts at the Department of Systems of Life Activity Provision, Rescue and Protection on Aircraft (Moscow, Russian Federation) (Vezirishvili et al., 1999; Roslyakova et al., 2000). Volunteers were treated with single and repeated doses of the preparation and subjected to exercises that simulated long monotonous fatigue-inducing activities. Methods of evaluation included questionnaires, computer tests, psycho-physiological and psycho-emotional tests, ophthalmological examinations, determination of medical parameters (heart rate, ECG pattern, respiration, blood pressure, etc.) and mathematical analysis of cardiac rhythm. The authors concluded that rodelim can be recommended for increasing mental and physical performance and working capacity under high load.

An interesting comparative study is available (Berdyshev, 1995) of the effects and modes of actions of preparations of Schizandra and Eleutherococcus taken by sailors working under stress during watch periods conducted at night or under unfavourable sea conditions. Various functional parameters were measured in two groups ($n = 357$) of sailors (all of similar age, sex, and duration and conditions of work) 30–60 min before treatment and immediately (within 30–60 min) after their watch. One group of subjects acted as controls throughout the study, whilst members of the second group were treated with a single dose of placebo or of a tincture of Schizandra (3 mL) or Eleutherococcus (4 mL) prior to their watch.

The results of this study (Tables 5 and 6) revealed that a single dose of Eleutherococcus gave rise to (i) a decrease in adrenal cortex activity and tonus of the sympathetic part of the autonomic nervous system, (ii) a pronounced increase in the tonus of the parasympathetic part of the autonomic nervous system, (iii) moderate intensification of energy metabolism with a practically unchanged respiratory coefficient, (iv) a tendency to intensification of oxidation–reduction processes in tissues (Rotter test), (v) a decrease in catabolic processes (decreases in vitamin C and total nitrogen excreted with the urine), (vi) an improvement in the balance of cortical processes, (vii) moderate intensification of excitation of the central nervous system, (viii) a reduction in the increase in body temperature, and (ix) an improvement in the activity of the cardiovascular system activity by virtue of a slower pulse rate and an increased pulse pressure. The increase in working ability observed following treatment with Eleutherococcus occurred in parallel with improved endurance to hypoxia and an enhancement in the parameters associated with non-specific resistance of the organism. It was thus concluded that Eleutherococcus is able to reduce excessive exertion of an organism by virtue of its effect primarily on the adrenal function and tonus of the autonomic nervous system (Berdyshev, 1995).

The results obtained following a single dose of Schizandra indicated the operation of a different mechanism in which increased working ability correlated directly with increased tonus of the CNS, the sympathetic adrenomedullar system and adrenal functional activity, together with intensified energy metabolism, catabolic processes and functional activity of the cardiovascular system (Tables 5 and 6). This was accompanied in turn by an increase in body temperature, a poorer endurance to hypoxia, and a decrease in some parameters associated with non-specific resistance of the organism. These facts indicate that the effect of Schizandra was occasioned, to a certain extent, through additional mobilisation of energy resources of the organism and a moderate stimulation of functional structures. It appears, therefore, that Schizandra has a gentle stimulating effect.

5.4. Central nervous system

One of the first studies carried out on healthy subjects (33 marines), in which the effects of SSE were compared with those of a decoction of German chamomile (as control), indicated that Schizandra did not exhibit anti-hypnotic and anti-narcotic effects unlike many other stimulants including phenamine and caffeine (Lazarev, 1946). The phytoadaptogen was, however, shown to induce a reduction in chronaxy following studies on neuromuscular excitability in 13 healthy subjects (Yefimov and Vlasova, 1945). In a case report on the effects of Schizandra on excitation and inhibition of reflexes in post-traumatic encephalopathia, it was suggested that the positive therapeutic effects of Schizandra are due to the correction of imbalance between excitation and inhibition of reflexes (Markova and Samoilova, 1954).

5.5. Blood cells and vascular system

On the basis of the levels of excitation, motility and magnitude of their vascular reactions (determined from plethysmograms and arterial pressure analysis), Batkin (1962) was able to divide 24 healthy subjects into three groups characterised by (i) optimal reactions (no dilatation of vessels on inhalation and strong prolonged vasospasm on exhalation), (ii) increased reactions (vasodilatation on inhalation and strong but short-lived vasospasm on exhalation), and (iii) decreased reactions (vasodilatation on inhalation and weak vasospasm on exhalation). Unlike phenamine and caffeine, which increased excitation in all three groups, Schizandra extract exhibited a corrective effect in that it increased excitation when it was decreased or insufficient, but decreased excitation when it was increased. Moreover, Schizandra exhibited no effect on arterial pressure.

Following a study involving 56 healthy subjects, Belikina and Prokofjeva (1959) reported that the effects of Schizandra on blood coagulation, platelet number, and prothrombin and coagulation factors are dependent on the treatment regime. Thus, administration of three doses of tincture increased all of these parameters, while simple stimulation of the mouth receptor had an exactly opposite effect. However, administration of ST to 70 pregnant women for 10 days prepartum gave rise to an increase in the blood coagulation system (Gaistruk and Taranovskij, 1968). Thus, whilst more than 12.4% of untreated women suffered from postpartum haemorrhages exceeding 350 mL, only 2.3% of the Schizandra-treated subjects presented this condition.

5.6. Mediators of stress-response

Nitric oxide (NO) is known to be a potent vasodilator, leading to an increase in blood flow, as well as an important mediator of the neuroendocrine–immune complex stress system. Moreover, NO is produced in large quantities during host defence and immunological reactions (Moncada et al., 1991) and, since it has cytostatic properties and is generated by activated macrophages, it is considered likely to have a role in non-specific immunity (Moncada, 1992). The innate immune system responds differentially to chronic stress occasioned by intensive exercise, with natural killer cell activity tending to be enhanced and neutrophil function being suppressed

Table 5
Effects of extracts of Eleutherococcus and Schizandra on organism functions of sailors following night watch duty conducted in middle latitudes

Parameters	Parameters measured after a 4 h night watch[a]		
	Control	Eleutherococcus	Schizandra
Simple sensorimotor response time (ms)	230 ± 1.0	226 ± 1.4*	212 ± 2.3*
Endurance to static effort (s)	24.9 ± 0.5	25.6 ± 0.6*	27.8 ± 0.6*
Tremometry (number of touches)	49.7 ± 0.4	47.9 ± 0.6	47.1 ± 0.5
Placement of numbers			
Numbers placed	15.1 ± 0.3	16.4 ± 0.5	18.9 ± 0.6
Number of mistakes	4.6 ± 0.1	4.2 ± 0.2	3.9 ± 0.3
Hench's test (s)	26.8 ± 0.5	28.9 ± 0.4*	26.5 ± 0.6*
Body temperature (°C)	36.30 ± 0.01	36.30 ± 0.01*	36.60 ± 0.02*
Heart rate (bpm)	66.2 ± 0.8	68.4 ± 0.9*	72.8 ± 1.1*
Systolic pressure (mmHg)	100 ± 0.8	104 ± 1.3*	108 ± 1.3*
Diastolic pressure (mmHg)	60.5 ± 0.7	62.0 ± 0.9*	70.0 ± 1.1*
Orthostatic test (bpm)	13.1 ± 0.6	14.1 ± 0.8*	18.2 ± 0.9*
Clinostatic test (bpm)	16.5 ± 1.0	16.4 ± 1.1	16.2 ± 0.8
Respiration rate (breaths/min)	12.4 ± 0.7	13.2 ± 0.6*	15.6 ± 0.7*
Diuresis (mL/h)	32.0 ± 2.0	33.5 ± 2.3*	41.5 ± 2.5*
Vitamin C excreted with urine (mg/h)	0.41 ± 0.02	0.43 ± 0.02*	0.62 ± 0.02*
17-Ketosteroids excreted with urine (mg/h)	0.59 ± 0.01	0.52 ± 0.02*	0.75 ± 0.03*
Vascular resistance			
Subjects with normal resistance (%)	58 ± 9.9	70 ± 9.1	61 ± 9.8
Subjects with sharply decreased resistance (%)	23 ± 8.4	14 ± 6.9	20 ± 8.0
Phagocytosis (%)	60 ± 2.4	71 ± 2.8*	53 ± 2.4*
Phagocytic index	13 ± 0.57	19 ± 0.62*	12 ± 0.55*
Rotter's test (min)	14.1 ± 1.3	13.6 ± 0.9*	10.5 ± 0.7*

[a] Within each row, parameter values associated with Eleutherococcus and Schizandra-treated subjects that are marked with an * are significantly different one from another ($p < 0.05$).

(Nieman, 1996). The acute immune response to prolonged aerobic exercise is associated with elevated stress hormone levels, particularly of cortisol, which induces neutrophilia, eosinopenia, lymphocytopenia and suppression of NK and T cell function, all of which occur during recovery from prolonged, high-intensity cardio-respiratory exercise. Increased neutrophil:lymphocyte and monocyte:eosinophyl ratios have been proposed as indices of physiological stress on the immune system after intensive exercise (Nieman, 1996).

In a placebo-controlled double-blind study aimed at determining the effects of Schizandra on stress, athletes ($n = 185$) were administered either placebo ($n = 48$), or Bryonia tablets ($n = 47$) at a dose of two tablets daily for 7 days, or Schizandra tablets ($n = 90$) containing 91.1 mg extract/tablet (extract standardised for schizandrin and γ-schizandrin at a level of 3.1 mg/tablet) at a dose of 2 tablets twice daily for 8 days (Panossian et al., 1999a). The group of athletes, which included jumpers, cyclists, boxers, wrestlers and weightlifters, were assayed before and after treatment and before and after exercise for salivary NO and blood cortisol, haemoglobin, neutrophil, eosinophil, lymphocyte, monocyte and erythrocyte levels, as well as for working capacity (maximal oxygen consumption/physical working criteria, PWC_{170} test), and endurance (i.e. number of jumps/min for boxers, number of throws of wrestling dolly for wrestlers, maximal weight jerk-lifted in 12 approaches for weightlifters, etc.). It was found that the level of NO in saliva freshly collected from beginners was strongly increased after heavy physical exercise, whilst in well-trained top-level athletes the level of salivary NO was not significantly altered following such exercises. Salivary NO might, therefore, constitute a measure of adaptation of an organism to heavy physical exercise. Treatment of athletes with either Bryonia tablets or Schizandra extract led to increases in both physical performance and the basal level of salivary NO in comparison with those taking placebo. However, following a period of heavy physical exercise, no further increase in salivary NO was observed in athletes treated with phytoadaptogens, whilst salivary NO levels were augmented in the control group of athletes. These results suggest that the phytoadaptogen-induced enhancement in physical performance could be due to a stimulatory effect on NO production, which would thus adapt the organism to heavy physical exercise.

With respect to plasma cortisol, administration of Bryonia tablets to beginners led to an increase in the basal value but induced a decrease in the level, compared with that of the placebo group, following heavy physical exercise. Thus, treatment with adaptogens has the same effect as that of chronic physical exercise in beginners by elevating both NO and cortisol levels in plasma and saliva. In well-trained athletes, however, the basal level of salivary cortisol was decreased following administration of Bryonia

Table 6
The values of correlation index between the effects of Eleutherococcus and Schizandra extracts on organism functions following day watch duty conducted under unfavourable (stressful) sea conditions

Parameters	Pair correlation index	
	Eleutherococcus	Schizandra
Urine 17-ketosteroids	−0.55	0.21
Eosinophils in the blood	0.42	−0.16
Energy metabolism	0.34	0.83
Rotter's test	−0.33	−0.59
Respiration coefficient	0.15	0.5
Tonus of the sympathetic adrenomedullar system	−0.27	0.78
Tonus of the parasympathetic nervous system	0.69	−0.21
Vitamin C excreted with urine	−0.22	0.4
Total nitrogen excreted with urine	−0.3	0.38
Breathing retention at exhalation	0.58	−0.35
Phagocytosis percentage	0.41	−0.24
Phagocytic index	0.53	−0.16
Vascular resistance	0.39	−0.4
Osmotic erythrocyte resistance	0.45	−0.27
CNS excitation	0.21	0.69
Excitation/inhibition balance in the CNS	0.48	−0.17
Heart rate	−0.36	0.49
Systolic blood pressure	0.18	0.45
Coefficient of the cardiovascular system endurance	−0.46	−0.29
Body temperature	−0.3	0.37

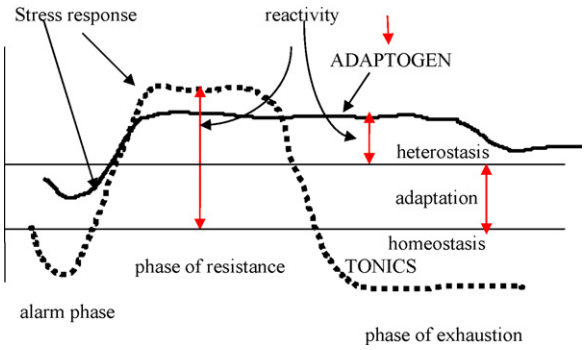

Fig. 8. Stress response and effect of adaptogens.

tablets and Schizandra extract, and a further decrease was observed following a period of heavy exercise (Panossian et al., 1999a). Moreover, the study revealed that both phytoadaptogens decreased the neutrophil:lymphocyte ratio and the monocyte:eosinophil ratio in treated athletes compared with the control group.

Considering the role of NO and cortisol in terms of the "switch on–switch off" concept of the stress-system, it can be concluded that: (i) stress, in the form of chronic and acute physical exercise, activates the formation of mediators of NO activation and cortisol suppression in the neuroendocrine system, (ii) phytoadaptogens exhibit a pro-stressor effect in that they activate the formation of NO and cortisol in blood plasma and saliva, and (iii) such activation adapts an organism to further heavy physical loading. In this respect adaptogens increase the production of both activating and deactivating messengers of the stress system, and they are challengers of the defence response of an organism. In other words, adaptogens increase the capacity of the stress system to respond to external signals at the higher level of the equilibrium—heterostasis (Fig. 8). In subjects, such as well-trained athletes, who have already adapted to chronic heavy physical exercise and exhibit increased basal levels of cortisol in blood or saliva, both physical exercise and adaptogens exert a somewhat opposite effect to stress in that they decrease of the levels of NO and cortisol, probably owing to their increased utilisation.

5.7. Local anti-inflammatory activity

Lupandin (1966) employed a simple inflammation test, involving the topical application of a few drops of 5, 10 or 20% phenol solution in benzene to induce a local elevation of skin temperature, in order to evaluate the anti-inflammatory effect of Schizandra. Phenol–benzene tests were performed on healthy volunteers ($n = 26$) prior to the application of SSP for 7 days (at a dose of 1.5 g/day) and 1 day after the termination of treatment. In all cases, temperatures at the sites of phenol application were significantly lower after treatment. Single dose treatments, however, gave rise to more distorted effects.

6. Clinical trials

6.1. Neurological disorders: effect on visual functions

Treatment with a preparation containing air-dried powdered fruits of Schizandra together with starch and glucose (1.6 g administered orally after 50–60 min adaptation to darkness) increased peripheral sensitivity of the retina in 15 subjects (Galochkina, 1948; Lebedev, 1971a). This treatment led to an increase in sensitivity to red light (600 nm) but decreased sensitivity to green light (520 nm), an effect which is possibly associated with parasympathomimetic effect of Schizandra.

Golovin and Golovina (1963) evaluated an electrophoretic treatment involving Schizandra on 592 patients with refraction anomalies. Micro-suspensions (30 and 60%) of the dried fruits of Schizandra were prepared by centrifugation followed by filtration of the supernatant through filter paper and activated charcoal, and applied to cotton buds that were placed behind the lower eyelid of the patient. Nickel electrodes were placed on the closed eyelids (cathode) and to the back of the head (anode) and a constant electric current (20 mA/kg) was applied for 30 min, following which the patient remained in a dark room with eyes closed for another 20 min. After a course of therapy involving 20 electrophoretic treatments, the acuteness of vision of patients with complicated and progressing myopia increased twofold to 0.06 and 0.09 (corresponding to treatment with 30 and 60% suspensions, respectively) without correctors, and to 0.55 and 0.78 (30 and 60% suspension, respectively) with correctors, whilst that of patients with medium and slight myopia returned almost to normal values with correctors. Similar results were obtained for patients with various types of astigmatism and hypermetropia. Although the applied therapy had no effect on the acuteness of vision in 10 patients (1.7%), all reported that the fatigability of their eyes during work disappeared and objects viewed were more distinct (Golovin and Golovina, 1963; Lebedev, 1971a). These results have been confirmed in a study of 176 children with progressive myopia and myopic astigmatism (Minejeva and Svindyukova, 1968). The improvement of acuteness of vision throughout the programme of electrophoretic treatments was evaluated in 30 of the patients and this revealed that the vision of 28 patients remained at the same level as that recorded at the end of the recommended three-course treatment of 20–25 days administered at intervals of 2 months. It should be mentioned that this electrophoretic treatment does not allow patients to dispense with the use of correctors; on the contrary, spectacles are recommended. Contraindications of the Schizandra treatment include glaucoma, hypertension, ocular tuberculosis, optic neuritis, engorged papillae, cataracts, haemorrhage, commotio retinae, amotio retinae and inflammation of the frontal part of the eyeball.

In a placebo-controlled study of 134 healthy subjects, Trusov (1953) showed that a single administration of SSP capsules (total dose 3 g) enhanced night vision and accelerated adaptation to darkness. Visual functions were evaluated 10–15 min prior to therapy, and sensitivity to light and acuteness of vision were measured again 1.5 h after treatment, whilst visual field margins for different colours were determined 3 h after drug administration. It was demonstrated that Schizandra increased visual acuity under low illumination and extended the visual field margins for both white and red light by 8–25°.

In a further study by the same author (Trusov, 1958a), visual sensitivity was evaluated in 150 healthy subjects as the time needed for recognition of an object in darkness, whilst adaptation to darkness was measured in terms of the level of darkness that just allowed recognition of an object. It was shown that a single administration of SSP at a dose of 3 g significantly increased visual sensitivity and adaptation to darkness in 90% of subjects. Treatment with the phytoadaptogen increased the rate of increase of visual sensitivity in as much as the time necessary for visual recognition of an object in darkness decreased from 32.3 s (prior to treatment) to 18.4 s (4.5 h after treatment). However, the final level of sensitivity was not altered by therapy with SSP, from which it was concluded that Schizandra affects the neural mechanisms of adaptation to darkness rather than the photochemical processes in the retina of the eye. This study also provides an indication of the mode of action of Schizandra, since pharmacological agents that mainly affect the brain cortex are known to induce equal alterations in visual

sensitivity in all regions of the visible spectrum (as is the case for Schizandra), while agents that act on the vegetative nervous system and/or hypothalamus–pituitary system have opposite effects on red and green vision (Trusov, 1958a,b).

Administration of 30 drops of a 10% tincture of Schizandra over a 40-day period to 25 women working on the production of computer devices gave rise to a significant beneficial effect on visual function (functional stability of colour vision, colour contrast, spectral sensitivity and critical fusion frequency), as well as on working performance and endurance. Typically, towards the end of a working day, the yield of good quality final product was typically reduced by 25–30% and the performance of work was twofold lower. Moreover, the workers complained about headache, fatigue, nervousness and sleeplessness caused by exhaustion. Treatment with Schizandra produced beneficial effects in 75% of subjects. After the first uptake of ST the asthenopia threshold to red and green colours improved, respectively, to 125 and 128%, the ability to distinguish between colours increased at the end of working day to 40–49% of the level at the beginning of the day, contrast sensitivity to red, green and blue was enhanced by *ca.* 1.5- to 2-fold in 92.5% of cases, and the level of spectral sensitivity to these colours increased by 45, 51 and 34%, respectively (Sosnova et al., 1984).

Therapy with SSP (at a dose of 1.5 g/day) led to expansion of the visual field in 46 patients with chronic chorioretinitis, retinal pigmentary degeneration, visual nerve atrophy and myopia (Sinovich and Akhmetova, 1958).

6.2. Other neurological disorders: effect on motor disturbances in patients presenting central and peripheral nervous damage

Treatment with SSP at a dose of 0.3 g/day for 3–4 weeks has been shown to produce a positive therapeutic effect in hemiparesis and flabby paralysis, but no effect was observed in spinal pareses, myopathia and myoplegia, cerebellar ataxia, and other syndromes (Zatonskaya and Serebryanik, 1958). It has been suggested that Schizandra could be used as a supporting agent in addition to the main chemotherapy.

6.3. Asthenia

In a trial involving more than 250 patients, tinctures, decoctions and tablets of Schizandra were found to be very effective in the treatment of general asthenia, exhaustion and reduced physical and mental performance, with recovery occurring typically within 2–10 weeks (Rossijskij, 1952a,b). The preparations of the phytoadaptogen exhibited a remarkable effect on a group of patients ($n = 200$) with nervous disorders, where an increase in general well-being and working capacity was observed, together with a reduction in sleepiness and flabbiness.

6.4. Stress-protective effect: recovery, mental performance and quality of life in pneumonia patients

It has been proposed that adaptogens could be used as remedies for improving the quality-of-life in any population of patients or healthy subjects. Members of this group of medications are innocuous agents that non-specifically increase the resistance of an individual against physical, chemical or biological factors ("stressors") by normalising their effect independent of the nature of the pathological state. Adaptogens have been used as adjuvants to other medicines in enhancing the curative effect in, for example, chronic pneumonia, chronic tuberculosis, vascular dystonia, and cancer (reduction of metastasis), and in reducing the debilitating effects of radiotherapy and chemotherapy. It is anticipated, therefore, that adaptogens may have a direct impact on most facets of physical health and psychological state and, moreover, may indirectly improve aspects of social and environmental domains.

In a double-blind, parallel-group, randomised (simple randomisation), pilot study, Chisan® (ADAPT-232; Swedish Herbal Institute, Åskloster, Sweden), a standardised fixed combination of extracts of *Rhodiola rosea*, *Schisandra chinensis* and *Eleutherococcus senticosus*, was evaluated for its efficacy as an adjuvant therapy for the improvement of the quality-of-life and recovery period of patients suffering from acute non-specific pneumonia and receiving a standard treatment (Narimanian et al., 2005). Sixty patients (males and females; 18–65 years old) received a standard treatment with cephazoline, bromhexine, and theophylline: in addition, one group of 30 patients received Chisan mixture whilst the second group of 30 patients received a placebo, each medication being taken twice daily from the beginning of the study for 10–15 days. The primary outcome measurements were the duration of antibiotic therapy associated with the clinical manifestations of the acute phase of the disease, together with an evaluation of mental performance in a psychometric test and the self-evaluation of quality-of-life (WHOQOL-Brief questionnaires), before treatment and on the 1st and 5th days after clinical convalescence. The mean duration of treatment with antibiotics required to bring about recovery from the acute phase of the disease was 2 days shorter in patients treated with Chisan compared with those in the placebo group. With respect to all quality-of-life domains (physical, psychological, social and ecological), patients in the Chisan group presented higher scores at the beginning of the rehabilitation period, and significantly higher scores on the 5th day after clinical convalescence, than patients in the control group. Clearly, adjuvant therapy with ADAPT-232 has a positive effect on the recovery of patients by decreasing the duration of the acute phase of the illness, by increasing mental performance of patients in the rehabilitation period, and by improving their quality-of-life. Both the clinical and laboratory results of the study suggested that Chisan (ADAPT-232) could be recommended in the standard treatment of patients with acute non-specific pneumonia as an adjuvant to increase the quality-of-life and to expedite the recovery of patients.

6.5. Stress-protective effect: prevention of chemotherapy-induced immunosuppression in cancer

Chemotherapy-induced immunosuppression represents a significant problem in cancer therapy. However, whilst cytotoxic chemicals decrease the state of non-specific resistance of an organism, adaptogens (by definition) exert the opposite effect. On this basis, a clinical trial of AdMax® (Nulab Inc., Clearwater, FL, USA), a fixed combination of the dried ethanol:water extracts from roots of *Leuzea carthamoides*, *Rhodiola rosea*, *Eleutherococcus senticosus* and fruits of *Schisandra chinensis*, on immunity in ovarian cancer patients has been conducted (Kormosh et al., 2006). Patients ($n = 28$) with stage III–IV epithelial ovarian cancer were treated with a single dose of 75 mg/m^2 cisplatin and 600 mg/m^2 cyclophosphamide. Peripheral blood was collected 4 weeks after chemotherapy, and levels of various subclasses of T, B and NK lymphocytes, together with the concentrations of the immunoglobulins (Ig) G, A and M, were determined. Mean numbers of the T cell subclasses CD3, CD4, CD5 and CD8 were increased in patients who received AdMax (270 mg a day) for 4 weeks following the chemotherapy in comparison with those who did not. Patients treated with AdMax also presented increased mean levels of IgG and IgM. The results obtained indicate that combinations of extracts from adaptogenic plants may boost suppressed immunity in ovarian cancer patients who are receiving chemotherapy.

6.6. Stress-protective effect: radioprotection of the fetoplacental system in pregnant women

The efficacy of a complex therapy, involving the administration of vitamins together with the adaptogens Eleutherococcus, Echinopanax, Aralia or Schizandra tincture, in the prevention of disorders of the fetoplacental system (FPS) in pregnant women living in a radionuclide-contaminated zone, has been assessed (Fedorova et al., 1994). Following an evaluation of the dynamics of the hormonal levels in the FPS, it was established that the prophylactic therapy improved the functional state of the fetal parameters (i.e. oestriol, hydrocortisone and embryonic α-fetoprotein) in 60% of cases, and of the placental parameters (progesterone and lactogen) in 43% of cases.

6.7. Stress induced disorders: gastric hyper- and hypo-secretion, chronic gastritis, stomach and duodenal ulcers

A preliminary indication that Schizandra was effective in the treatment of gastritis was provided by Masyuk (1949) who mentioned that a preparation of the seed material increased gastric acidity in summer, but in winter gastric hypersecretion was normalised in 8 patients. In a later study involving 26 subjects (7 with hyperacidity, 10 with hypoacidity and 9 with normal gastric secretion), Amitina and Vodianova (1958) demonstrated that SSP applied at a dose of 2 g/day over a period of 1–3 weeks normalised gastric secretion. Lapajev (1958) studied a population (n = 172) of individuals (comprising 90 presenting hyperacidity, 71 exhibiting hypoacidity and 11 with normal gastric secretion) of which 51 suffered from gastritis, and found that on treating 82 of the patients with SSP (0.5 g, 3 times a day), gastric acidity was normalised (n = 8) or decreased (n = 29) in hyperacidic patients, and normalised (n = 12) or increased (n = 14) in hypoacidic patients. Symptomatic improvements were observable within the first 3–5 days of the treatment, and by the 25th day of medication 17 patients had improved significantly and 64 had attained total recovery. Similar results were achieved in the control group where a complex treatment involving diet therapy, physiotherapy and chemical therapy had been employed. In a later study, the same author (Lapajev, 1961) presented results of 216 patients (109 hyperacidic, 94 hypoacidic, 13 normal gastric secretion) of which 63 patients had chronic gastritis. In this case, 83 patients were treated with Schizandra and gastric acidity was normalised in 62% and decreased in 15% of hyperacidic patients, and was normalised in 35%, and increased in 40% of hypoacidic patients. A total recovery was achieved for 67% of the patients treated, and improvements were observed in 31% of patients; similar results were achieved in the control group in which the complex treatment outlined above was again employed.

It has been reported that Schizandra fruit juice strongly increases gastric secretion, total acidity and free hydrochloric acid in the gastric juice of patients with sub-acidic gastritis, with the maximum effect becoming apparent just 15 min after administration of the phytoadaptogen (Lapajev, 1967a,b). More detailed *in vitro* studies revealed that SSP and its decoction decreased total acidity and free hydrochloric acid content in the stomach juice, whilst dried fruit, or a decoction thereof, and (more especially) fruit juice elicited the opposite effect (Lapajev, 1967a,b, 1969). Moreover, Schizandra juice augments the decreased uropepsin content and chloride anion concentration in the blood of patients with stomach hyposecretory activity (Lapajev and Mosyakova, 1970). In contrast, SSP preparations normalised hypersecretion and stomach motility and had a significant curative effect in hyperacidic gastritis (Lapajev, 1958, 1961, 1969).

The efficacy of SSP (at a daily dose of 1 g before meals over a period of 35 days) on stomach and duodenal ulcers were evaluated in groups of up to 140 patients presenting chronic (71.7%) or acute (28.3%) ulceration, some of whom had been ill from between 5 and 10 years whilst others had suffered from the syndrome for only 1–5 years (Lapajev and Sokolova, 1970; Lapajev, 1978). Clinical symptoms (i.e. the absence of pain, dyspepsia, etc.) and the disappearance of cicatrisation were used in the assessment of the efficiency of treatment. Some 75% of patients experienced improvement in the first 10 days of treatment with Schizandra, in that pains in the epigastric area were reduced, the appetite recovered, dyspeptic symptoms disappeared and there was a decrease in stomach locomotor activity. Following a 35-day course of Schizandra therapy, ulcers had healed in 135 of 140 patients (96.5%). In contrast, only 61% of patients (n = 100) who had received treatment with vicaline reported relief of pain within the 10 days, and at the end of the treatment period ulcers had healed in only 84% of these patients. A follow-up study of 90 of the Schizandra-treated patients revealed that only 9 had experienced recurrent episodes of ulceration within a period of between 1 and 6 years from the original treatment (Lapajev, 1978).

SSE has been shown to both increase and reduce cholinesterase activity and the content of 17-hydroxycorticosteroids, and also to normalise vascular tonus in patients with gastric and duodenal ulcers (Lapajev, 1978). However, Schizandra is contraindicated for patients with stomach and duodenal ulcers who are known to present an excitable type of vascular response, since even medium therapeutic doses could lead to the development of neurotic vascular reactions (Surovtseva et al., 1958).

6.8. Emotional stress induced psychiatric disorders

6.8.1. Neurosis

In a pilot clinical study in which the effects on neurasthenic patients (n = 95) of pantocrin and tinctures of Schizandra seeds and Ginseng root were evaluated, administration of Tinctura Seminum Schizandrae (10%; 15 drops for 25–28 days) was found to be highly efficacious in the treatment of general weakness, lack of appetite, insomnia, irritability and headache. Whilst 55% of the control group of neurasthenic patients exhibited such symptoms, they disappeared almost completely in the Schizandra group (Farutina, 1951). Moreover, compared with the control group, the muscular force of the hands of subjects in the Schizandra group increased 2.5-times, the vital lung capacity increased by 19% (*cf.* 3% in the control group), and blood haemoglobin increased by 6% (cf. 1.6% in a control group receiving standard medications).

6.8.2. Psychogenic depression, astheno-depressive states, schizophrenia and alcoholism

Positive therapeutic effects of Schizandra preparations on asthenic and astheno-depressive states (particularly in exogenous depression) in psychiatric diseases have been reported by several groups (Sivertsev, 1946, 1950; Staritsina, 1946; Leman, 1952; Zakharov, 1956; Galant et al., 1957; Galant, 1958; Romas, 1958, 1967). Thus, administration of Schizandra (fruit and seed tincture, 1:5, 90% ethanol) for 16–40 days produced a stimulation of the CNS in all 40 patients with asthenia and depressions of psychogenic or somatic origin (Leman, 1952). An improvement in dark vision and a rush of blood to the skin and extremities was observed in almost all patients, whilst cold endurance increased in 26 patients. Twenty-two subjects became energetic and physically more active and reported pleasant warmth all over their bodies accompanied by an improvement in mood, the disappearance of the feeling of hunger and fatigue, and normalisation of the night sleep pattern. In seven patients, the first two or three doses of medication induced a strong effect (i.e. increased anxiety, fear, too rapid flow of thought, unpleasant heat over the whole body and face,

restlessness, loss of appetite, insomnia and tendency to hysteria), a state that continued for 8–24 h, after which the patients achieved an almost total recovery with the same improvements as in the other 22 patients. These results suggest that Schizandra acts in the long term as a stimulant of the cerebral cortex inducing feedback inhibition of the subcortex. It was concluded that Schizandra therapy can be indicated in asthenia and depressions of psychogenic aetiology (so-called "exogenous" depressions) or those related to excessive fatigue, somatic and nervous exhaustion. However, in depressions of organic aetiology ("endogenous" depressions), asthenia, narcoleptic and amnesic syndromes, the phytoadaptogen can only relieve the symptoms. One of the advantages of Schizandra treatment is the absence of side effects. Moreover, tolerance to Schizandra is many times greater than tolerance to caffeine or phenamine, and the effect of the medication is not lowered over a prolonged period of treatment. However, hot weather or constant exposure to a warm environment can be contraindications for the administration of Schizandra.

In another study, patients (n = 10) with astheno-depressive syndrome (ADS), characterised by sleepiness, flabbiness, inactivity, fatigue, blue mood, etc., attained full recoveries after 10 days of treatment with Schizandra (0.5 of a tablet before breakfast, and 0.25 before lunch and dinner) (Zakharova, 1948; Rossijskij, 1952a,b). However, in patients with schizophrenia (n = 8), psychopathy with ADS (n = 3) and organic CNS with ADS (n = 8), the astheno-depressive syndrome was eliminated but the other signs of disease were not affected. Furthermore, treatment with Schizandra was negative in patients with psychosis and hysteria (Zakharova, 1948; Zakharov, 1956). Conversely, Galant et al. (1957) claimed total recovery in psychosis following a trial involving the administration of SSP over a period of 10 days (0.5 g, three times a day) to 36 patients (19 with schizophrenia, 6 with reactive psychosis, 4 with alcoholic psychosis, 3 with involutional depression, and 4 with psychopathy) presenting astheno-depressive syndrome. However, the treatment showed no effect in psychopathy, whilst in the schizophrenic group, six patients recovered, seven patients showed improvement and in six (the hardest) cases the treatment was ineffective.

In a series of clinical trials involving 60 patients with mental disorders, Romas (1958, 1960, 1962) reported that Schizandra was effective in eliminating catatonic stupor in a group of 31 patients diagnosed with various forms of schizophrenia, i.e. simple (n = 4), paranoid (n = 11), catatonic stupor (n = 14), and catatonic excitation (n = 2), but was either not effective or had a negative effect on the other forms of schizophrenia. Moreover in maniacal depressive psychosis (n = 9) Schizandra decreased depression and associated stupor, but did not alleviate the hypomaniacal state, whilst in hallucinogenic paranoidal schizophrenia and alcoholic hallucinosis the phytoadaptogen promoted the disappearance of hallucinations and alcoholic deliria.

The same author also evaluated the effects of a tincture of Schizandra berries on 41 patients suffering from schizophrenia and 197 individuals presenting chronic alcoholism (Romas, 1967). In this study, vascular (alterations in blood flow in the palms of the hands) and pupillary reactions were measured using, respectively, a plethysmograph and a visual pupillometer, and conditioned reflexes were studied in order to determine the effects on the CNS. It was concluded that Schizandra activates these reactions in normal individuals, whilst in patients presenting schizophrenia or chronic alcoholism, in which the reactions are comparatively suppressed, the levels are returned to normal. As a result, the patients became calmer, more sociable and gregarious, free of emotional tension and anxiety, showed a willingness to work and presented a mood that was generally good. Furthermore, patients with hallucinogenic-paranoidal schizophrenia ceased to suffer from hallucinations, whilst fatty skin of the face disappeared in patients with catatonic stupor, and this was accompanied by an augmentation of face mimicry and general activity. From this work it was concluded that for patients suffering from simple and hallucinogenic-paranoidal schizophrenia, paranoidal schizophrenia, and catatonic schizophrenia, the optimal dosages of the tincture were in the region of 15–25, 5–15, and 5 drops, respectively. On the basis of observations relating to 15 schizophrenic patients, Zakharov (1956) concluded that administration of two doses of tincture per day was optimal and, since prolonged treatment could bring about a negative effect, the duration of the course of medication should be determined on an individual basis. These studies also confirmed that the results of treatment with Schizandra were better in patients with a short manifestation of the disease than in chronic patients (Zakharov, 1956; Romas, 1967).

Lastovetskij and Romas (1963) have demonstrated that activity of the secondary signalling nervous system and its interaction with the primary signalling nervous system were considerably activated in Schizandra-treated schizophrenia patients (n = 32) and in chronic alcoholics (n = 16). Thus, Schizandra intensified the development of conditioned reflexes to one or two parameters of the geometrical figures presented to the subjects, and verbalisation of the action by the subjects was also improved. Moreover, treatment increased associative process in the subjects and improved the quality of associations, as was shown by an increase in the number of higher verbal responses and a decrease in the number of lower responses.

It is particularly noteworthy that, besides intensifying the excitability of the brain centres in schizophrenia patients and in chronic alcoholics, Schizandra has been shown to increase the reactivity of the organism to insulin, sulphadiazine and apomorphine (Romas, 1962, 1967). Thus, administration of apomorphine together with Schizandra frequently eliminated or decreased addiction to apomorphine and, at the end of the treatment, a stable conditional emetic reflex developed in most chronic alcoholics. Another interesting finding, which seems to be of great practical importance, is that the combination of Schizandra with tranquillisers or antidepressants (such as sibazon, amitriptyline, relanium, etc.) was very effective in the elimination of their side effects. Thus, the development of headaches, dizziness, flaccidity, xerostomia, bowel and urinary disorders were observed in 23 out of 39 patients (53.5%) with neuromental disorders of exogenous-organic genesis following increased doses of amitriptyline (from 50 to 75 mg), while in Schizandra-treated patients a similar effect was observed in only 4 out of 172 patients (1.9%). Combined administration of tranquillisers and the adaptogen allowed the use of optimal doses of the drugs in 96% of patients whilst it was possible in only 16% of control patients ($p < 0.001$) (Sudakov et al., 1986)

In summary, it may be concluded that for healthy subjects in a state of fatigue, Schizandra can be recommended as a tonic since it decreases drowsiness and flabbiness, and improves the general mood and appetite. Schizandra can also be used in psychiatric practice as a symptomatic agent against astheno-depressive states, independent of the nature of the disease, with the advantages that it causes no negative effects on the somatic state of the patient and produces no changes in blood and urine, but rather arterial blood pressure is normalised regardless of whether it was originally elevated or reduced with respect to the norm. Schizandra can be used in the treatment of psychoses as a stimulant without harmful side effects, but in some cases acceleration and appearance of psychotic symptoms have been noted. The optimal duration of treatment with the phytoadaptogen will be different for each patient and must be determined on a per case basis. Although Schizandra has few contraindications, avoidance of prolonged exposure to heat is recommended, and the medication should not be used with patients presenting certain mental conditions including (a) psychomotor

excitement, (b) a state of fear, anxiety, or agitated anguish, and (c) prolonged hallucinative-delirious states. Additionally, combination of Schizandra with tranquillisers or antidepressants (sibazon, amitriptyline, relanium, etc.) reduces the side effects of these drugs and allows their application at optimal doses.

6.9. Infectious and chronic diseases

6.9.1. Influenza

An investigation of a group of 1200 patients over an 8 month period revealed that 1162 patients who took infusions of Schizandra leaves caught no colds, whereas 38 patients who terminated the medication typically contracted infectious respiratory diseases three or four times during the same period (Masyuk, 1949). In studies conducted during an influenza epidemic in 1969, Lebedev (1970a,b, 1971a,b) reported that administration of ST at a dose of 25 drops/day) resulted in a significant decrease in the morbidity rate among school children ($n = 115$, control group $n = 231$) and factory workers ($n = 300$, control group $n = 400$). In the case of school children, the morbidity rate in the control group was 19.5%, whilst that of a group that had been treated with Schizandra for 1 month decreased to 12.5%, a fall of 35.9%. Continuation of the treatment for a further period of 1 or 2 months gave rise to further reductions in morbidity of 65.1 and 64.4%, respectively (Lebedev, 1970a,b). The duration of infection and the clinical manifestations of the illness were observed to be less severe in the Schizandra group. In particular, Schizandra was particularly efficacious in the prevention of angina and acute respiratory disease (ARD) in influenza patients, e.g. no cases of angina were observed in boys of the Schizandra group. Similar results were obtained in respect of the groups of factory workers in which a decrease in morbidity rate and loss of working days of *ca.* twofold was recorded during the period of Schizandra uptake and for the succeeding 2 months (Lebedev, 1970b). Throughout these studies, no adverse effects of Schizandra were detected.

Shadrin et al. (1986) studied the possible effect of Schizandra on the stimulation of post-vaccination immunity in association with the administration of live or inactivated influenza vaccine to 292 male naval recruits Administration of SSE (30 drops with tea, twice a day for 1 week pre- and 2 weeks post-vaccination) did not significantly affect the frequency of seroconversion to vaccinal virus A (Khabarovsk, 1/77, HINI) in subjects vaccinated with live or inactivated di-vaccines (HINI + H3N2) *versus* the control group (who received placebo tea). Moreover, the groups did not differ in respect of the mean titre or of the average rate of increase in titre of antibodies, and no immune-stimulating effects of the phytoadaptogen were observed, e.g. the frequency of influenza and of ARD in groups receiving SSE did not differ from those of the control group. However, the frequency of typical complications of influenza (pneumonia, bronchitis, maxillary sinusitis and otitis) in the Schizandra-treated group was twofold lower (but statistically insignificant; $p > 0.05$) compared with the control group.

6.9.2. Chronic sinusitis, otitis, neuritis and otosclerosis

In a study involving 289 patients suffering from different forms of chronic sinusitis, 72% of the 89 subjects treated with Schizandra and levamisole (decaris) attained a full clinical recovery compared with only 46% in a control group receiving the traditional treatment (Konoplev, 1989). Furthermore, the decreased numbers of circulating T-lymphocytes and increased levels of B-lymphocytes in the blood were returned to normal in, respectively, 77 and 82.8% of patients treated with Schizandra and levamisole compared with only 14 and 68%, respectively, in the groups who had received conventional therapy. However, a group of patients with chronic purulent and polypous-purulent sinusitis proved to be an exception since, by the end of the treatment, their immunological status had failed to normalise. In patients presenting chronic otitis and chronic catarrhs ($n = 37$), treatment with Schizandra increased tonal hearing, but not vocal hearing, in 25–30% of cases, but was found to be ineffective in the treatment of neuritis of hearing nerves and hardness of hearing (Rokhlin, 1958).

6.9.3. Pneumonia

Treatment of severe and complicated forms of pneumonia with Eleutherococcus ($n = 46$) and tincture of Schizandra fruit ($n = 40$) resulted in the rapid disappearance of symptoms of intoxication (i.e. after only 5–6 days of treatment compared with 8–9 days with routine therapy) and in much (1.4-fold) shorter periods of elevated body temperature in elderly patients (Pavlushchenko, 1981).

6.10. Acute gastrointestinal diseases

In a group of children ($n = 100$) aged between 1 and 2 years and suffering from dysentery, therapy with dysentery bacteriophage plus tincture of Schizandra ($n = 50$) gave a survival rate of 76% compared with 42% in the control group ($n = 50$) treated with dysentery bacteriophage alone (Zuzanova and Bakhtina, 1954; Lupandin and Lapajev, 1981). SSP was also effective in the treatment of acute enterocolitis with clinical symptoms typical of light and mild forms of acute dysentery ($n = 400$) (Pelishenko, 1972). In the treatment of acute infections of the gastrointestinal tract, best results were obtained in groups of patients treated with Schizandra alone or with a combination of Schizandra and tetracycline, compared with patients who received antibiotic treatment alone.

6.11. Wound healing

In order to asses the effect of Schizandra on wound healing, a total of 160 patients (80% of whom were aged between 5 and 20 years) suffering from trauma- or varicose vein dilatation-induced trophic ulcers, or from slowly granulating wounds, were subjected to three different forms of treatment (Walter, 1955, 1956). One group ($n = 30$) received topical application of a 20% water extract of SSP plus per oral administration of SSP at a rate of 3 g twice per day for 20–60 days, another group ($n = 90$) received Schizandra treatment in combination with surgical procedures, whilst a control group 3 ($n = 40$) received common complex therapy including tissue therapy, blood transfusion, UV-irradiation, perinephrial novocaine blockage and massage. The most effective treatment involved a combination of surgery and medication with Schizandra, which resulted in the healing of 97.7% of wounds and for 92.5% of these patients recurrent ulceration did not occur. The use of Schizandra alone was somewhat less effective (86.6% of ulcers healed but only 50% remained stable), whilst the complex therapy resulted in a healing rate of 92.5%.

6.12. Allergic dermatitis

The application of a medication containing tinctures of Schizandra, Aralia and Lagochilus for the treatment of allergic dermatosis has been recommended (Golysheva et al., 1991).

6.13. Cardiovascular system disorders

Normalisation of arterial blood pressure and cardiac rhythm in hypertensive and hypotensive patients ($n = 23$) presenting either tachycardia or bradycardia was achieved following administration of tinctures of seeds and fruits of Schizandra over periods of 15–40 days (Leman, 1952; Agejenko and Komissarenko, 1960;

Lupandin and Lapajev, 1981). The treatment had no effect, however, on healthy subjects (control group $n = 13$).

Following a study involving 1162 patients, Masyuk (1949) reported that regular therapy over 8 months with 1% infusions of Schizandra leaves increased working capacity, reduced sleepiness and normalised the blood pressure of 116 hypotensive and 72 hypertensive patients (the other 974 patients had normal blood pressure). After 1 month of treatment, 31 of the116 patients remained with hypotension and 6 of the 72 patients still exhibited hypertension, hence the overall recovery rate for patients with these disorders was 77%. A 10% tincture of Schizandra administered at a dose of 30–40 drops, three times per day for 10 days, was effective in the treatment of arterial hypotension in pregnant woman ($n = 70$) (Gaistruk and Taranovskij, 1968). The phytoadaptogen increased the arterial and venous pressure by 10–20 mmHg, intensified the blood flow velocity by 5–10 s, increasing the speed of the pulsatory wave to 468 m/s, and decreased the blood pressure in the temporal artery by 5–10 mmHg. Moreover, oscillometric tests revealed an overwhelming tendency towards increased vascular tension and a decrease in the oscillometric index in the medicated patients. In addition, no complaints of headache or noises in the ears were recorded following the treatment (Agejenko and Komissarenko, 1960; Lebedev, 1971a; Lupandin and Lapajev, 1981). Tablets and tinctures of Schizandra seeds or fruits have been recommended in hypotension for the relief of asthenic symptoms (Lidskij, 1959).

Belikina and Prokofjeva (1959) have claimed that administration of three doses of Schizandra extract to 56 healthy subjects increased the number of blood platelets. In the case of patients presenting thrombocytopenia, however, the effect of Schizandra fruit juice is apparently remarkable leading to a threefold to eightfold increase in blood platelets and full recovery of the subjects (Lapajev, 1965).

6.14. Adverse events/safety profile

Generally, schizandrin has not been found to induce adverse effects in healthy humans. Of a total of 153 subjects to whom schizandrin was administered in doses of 3.6 mg ($n = 17$), 5 mg ($n = 44$), 10 mg ($n = 47$) or 20 mg ($n = 45$), only four subjects experienced excitation and three complained of depression (Lebedev, 1967). Within a group of 1200 patients studied by Masyuk (1949), 1162 individuals had been taking infusions of Schizandra leaves regularly for 8 months with no drug dependency or significant adverse effects. Schizandra treatment had alleviated exhaustion, fatigue and sleepiness, had increased working capacity and had reduced the need for a midday rest. Only 38 patients (3.3%) had ceased taking Schizandra because of excitation of the central and vegetative nervous systems. In another study, no adverse effects of Schizandra were detected in 415 patients taking SSE for 1 month during influenza epidemic (Lebedev, 1970a,b).

Schizandra seems to be a very well tolerated herb that has also been tested on cancer patients without any evidence of interaction with other potential drugs (Kormosh et al., 2006). Thus, on the basis of the information available, and despite some *in vitro* data reporting a CRY enzyme interaction, there is currently no suggestion that the traditionally used Schisandra preparations possess any clinically relevant herb–drug interaction potential.

7. The use of *Schisandra chinensis* in the official medicine of Russia (former USSR)

The established medicinal use of Schizandra preparations in the former USSR is reflected in the major pharmacological guides and medical textbooks. In order to exemplify this aspect, three main sources have been selected.

The most authoritative work on Russian medicine aimed at physicians and pharmacists is the *Medicinal Drugs—Manual on Pharmacotherapy for Doctors* compiled by Mashkovskij (1978, 2000). This manual has been updated regularly over many decades and covers every drug approved by the Ministry of Health. The manual lists *Schisandra chinensis* as an anti-fatigue (stimulant drug) and its medicinal indication, which has remained unchanged since the 8th edition of 1978 (Mashkovskij, 1978) to the most recent volume of 2000 (Mashkovskij, 2000), states: "*It has a stimulating effect on the central nervous system (CNS), the cardiovascular system and the respiratory system. In the event of mental exhaustion it increases the capacity of work. Taken under physical strain, physical and mental fatigue, in the event of extreme drowsiness, etc. Prescribed orally in the form of tincture*."

Another important and frequently used textbook of Russian medicine is *Pharmacognosy—With Fundamentals of Biochemistry of Medicinal Herbs* by Muravijeva (1978, 1991), which provides the following information: "*Stimulating effects of Schizandra fruits and seeds are widely known. They are used to produce tinctures. Working capacity increases "softly" without subjectively felt excitement. General strengthening effect of Schizandra on human organism is also very important* (*increase in body weight, muscular force, vital lung capacity, increase in resistance to unfavourable factors of the environment*)."

A third source is *Medicinal Plants of the USSR and their Use* by Turova (1974) in which the following paragraph appears: "*Clinical studies of Schizandra effect on visual functions of the eye are of special interest (method: electrophoresis). Acuteness of vision increased to some extent in all patients with different visual disorders under the effect of Schizandra tincture. Since more than half of the patients had complicated progressive myopia with very low acuteness of vision, this therapy (electrophoresis-Schizandra) can be considered highly effective. The results on 607 patients are discussed in this paper. The study was carried out at the Ophthalmologic Department of the Area Hospital in Ulianovsk. Based on pharmacological and clinical studies it is concluded that Schizandra has a tonic and stimulatory effect during fatigue and increases the mental and physical work capacity. As a psychostimulant its action is softer than phenamine and is effective in asthenia. Preparations from Schizandra increase the perplexed and central visual sensitivity. The absence of any essential side-effect or cumulative action allows for placing Schizandra in the category of the most valuable stimulating drugs*."

In these textbooks, and in various others, *Schisandra chinensis* is described as a stimulant and an adaptogen, whilst the bibliographical documentation provided in this review clearly demonstrates the established medicinal use of Schizandra over a period of more than three decades. In order to acquire more precise information about the quantitative use of Schizandra preparations in Russian medicine, a more detailed statistical study would be necessary. In this context, however, an indication of the usage of the drug may be derived from the domestic distribution of the dried raw material of Schizandra from the All-Union Distributor "Centrosoyuz". During the 1970s, it is estimated that some 5–10 tons of the raw plant material were consumed per year suggesting the consumption of over one million bottles of prepared medication annually.

Throughout the extensive body of Russian scientific research published in the form of articles in Russian scientific journals, PhD dissertations and proceedings of scientific conferences, etc., there runs a consistent theme regarding the effectiveness of Schizandra as an adaptogen and an anti-fatigue agent. This view is in line with the current notion of a well-established medicinal use of *Schisandra chinensis* with regard to its recognised efficacy and extensive use over more than 30 years in the official Russian medicine.

Conflict of interest

The authors are associated with the Swedish Herbal Institute, a company that researches and commercialises Schisandra-derived functional products.

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